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NEWS	4	FEB 28	BABS - Current-awareness alerts (SDIs) available
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NEWS	6	MAR 03	REGISTRY/ZREGISTRY - Sequence annotations enhanced
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NEWS	8	MAR 22	KOREAPAT now updated monthly; patent information enhanced
NEWS	9	MAR 22	Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS	10	MAR 22	PATDPASPC - New patent database available
NEWS	11	MAR 22	REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS	12	APR 04	EPFULL enhanced with additional patent information and new fields
NEWS	13	APR 04	EMBASE - Database reloaded and enhanced
NEWS	14	APR 18	New CAS Information Use Policies available online
NEWS	15	APR 25	Patent searching, including current-awareness alerts (SDIs), based on application date in CA/CAplus and USPATFULL/USPAT2 may be affected by a change in filing date for U.S. applications.
NEWS	16	APR 28	Improved searching of U.S. Patent Classifications for U.S. patent records in CA/CAplus
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NEWS	23	JUL 01	MEDICONF removed from STN
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NEWS	25	JUL 13	SCISEARCH reloaded
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NEWS	28	AUG 11	STN AnaVist workshops to be held in North America
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=> s GHRH or growth hormone releasing hormone or (GHRH(W)VARIANTS)
L1 15147 GHRH OR GROWTH HORMONE RELEASING HORMONE OR (GHRH(W) VARIANTS)

=> s l1 and treatment
L2 3414 L1 AND TREATMENT

=> s l1 (amin?(w)acid(w)substit?)
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=> s l1 and (amin?(w)acid(w)substit?)
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L3 60 L1 AND (AMIN?(W) ACID(W) SUBSTIT?)

=> s l2 and (livestock or cow? or cattle or bovine or sheep or ovine or human)
L4 2233 L2 AND (LIVESTOCK OR COW? OR CATTLE OR BOVINE OR SHEEP OR OVINE OR HUMAN)

=> s l4 and (gh or growth hormone)
L5 2206 L4 AND (GH OR GROWTH HORMONE)

=> d

L5 ANSWER 1 OF 2206 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2005:289451 BIOSIS
DN PREV200510080729
TI Acromegaly due to a **growth hormone-releasing hormone**-secreting intracranial gangliocytoma.
AU Isidro, M. L.; Diaz, P. Iglesias; Matias-Guiu, X.; Cordido, F. [Reprint Author]

CS CHU Juan Canalejo, Dept Endocrinol, As Xubias 84, La Coruna 15006, Spain
fernando_cordido@canalejo.org
SO Journal of Endocrinological Investigation, (FEB 2005) Vol. 28, No. 2, pp. 162-165.
CODEN: JEIND7. ISSN: 0391-4097.
DT Article
LA English
ED Entered STN: 4 Aug 2005
Last Updated on STN: 4 Aug 2005

=> s l5 and (treatment with)
L6 1711 L5 AND (TREATMENT WITH)

=> s l5 not py>2001
L7 1809 L5 NOT PY>2001

=> dis search
'SEARCH' IS NOT A VALID FORMAT
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'L30' IS NOT A VALID FORMAT
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'REMOVE' IS NOT A VALID FORMAT
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'FREE' IS NOT A VALID FORMAT
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'L30' IS NOT A VALID FORMAT
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L7 ANSWER 1 OF 1809 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Direct modification of somatotrope function by long-term leptin **treatment** of primary cultured **ovine** pituitary cells.

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L8 717 DUPLICATE REMOVE L7 (1092 DUPLICATES REMOVED)

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L3 ANSWER 1 OF 60 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:269390 BIOSIS
DOCUMENT NUMBER: PREV200400265983
TITLE: Molecular cloning and characterization of a gonadotropin-releasing hormone receptor in the guinea pig, Cavia porcellus.
AUTHOR(S): Fujii, Yukiko; Enomoto, Masahiro [Reprint Author]; Ikemoto, Tadahiro; Endo, Daisuke; Okubo, Kataaki; Aida, Katsumi; Park, Min Kyun
CORPORATE SOURCE: Grad Sch SciDept Biol SciBunkyo Ku, Univ Tokyo, 7-3-1 Hongo, Tokyo, 1130033, Japan
ss37180@mail.ecc.u-tokyo.ac.jp
SOURCE: General and Comparative Endocrinology, (April 2004) Vol. 136, No. 2, pp. 208-216. print.
CODEN: GCENA5. ISSN: 0016-6480.
DOCUMENT TYPE: Article
LANGUAGE: English
OTHER SOURCE: DDBJ-AF426176; EMBL-AF426176; GenBank-AF426176
ENTRY DATE: Entered STN: 26 May 2004
Last Updated on STN: 26 May 2004
AB Guinea pig gonadotropin-releasing hormone (gpGnRH) is predicted to have a unique structure among all known forms of GnRH molecule (Endocrinology 138 (1997) 4123) and it is of great interest to determine whether the unique structure of gpGnRH is manifested in the characteristics of the guinea pig GnRH receptor. In the present study, we isolated a full-length cDNA for a GnRH receptor from the pituitary gland of the guinea pig. The putative guinea pig GnRH receptor protein has an amino acid identity of 79-87% with mammalian type 1 GnRH receptors. The amino acid residues which have been demonstrated to be important for ligand binding and signal transduction were conserved in the guinea pig GnRH receptor. However, there are several specific **amino acid substitutions** among mammalian type 1 GnRH receptors. Moreover, thou h the guinea pig has generally been classified as a rodent, the putative GnRH receptor protein did not have some rodent-specific characteristics. Total IP assays demonstrated that the cloned guinea pig GnRH receptor is a functional GnRH receptor and that it shows different preference of ligand sensitivities from the rat GnRH receptor.

L3 ANSWER 2 OF 60 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:152522 BIOSIS
DOCUMENT NUMBER: PREV200100152522
TITLE: Molecular cloning of **growth hormone-releasing hormone**/pituitary adenylyl cyclase-activating polypeptide in the frog Xenopus laevis: Brain distribution and regulation after castration.
AUTHOR(S): Hu, Zhongting; Lelievre, Vincent; Tam, Jimmy; Cheng,

Jennifer W.; Fuenzalida, Gabriel; Zhou, Xinrong; Waschek, James A. [Reprint author]
CORPORATE SOURCE: Department of Psychiatry, University of California, 760 Westwood Plaza, 68-225 NPI, Los Angeles, CA, 90024, USA jwaschek@mednet.ucla.edu
SOURCE: Endocrinology, (September, 2000) Vol. 141, No. 9, pp. 3366-3376. print.
CODEN: ENDOAO. ISSN: 0013-7227.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Mar 2001
Last Updated on STN: 15 Feb 2002

AB Pituitary adenylyl cyclase-activating peptide (PACAP) appears to regulate several neuroendocrine functions in the frog, but its messenger RNA (mRNA) structure and brain distribution are unknown. To understand the potential role of PACAP in the male frog hypothalamic-pituitary-gonadal axis, we cloned the frog Xenopus laevis PACAP mRNA and determined its distribution in the brain. We then analyzed the castration-induced alterations of mRNA expression for PACAP and its selective type I receptor (PAC1) in the hypothalamic anterior preoptic area, a region known to regulate reproductive function. The PACAP mRNA encodes a peptide precursor predicted to give rise to both GH-releasing hormone and PACAP. The deduced peptide sequence of PACAP-38 was nearly identical to that of human PACAP with one **amino acid substitution**.
Abundant PACAP mRNA was detected in the brain, but not several other tissues, including the testis. In situ hybridization revealed strong expression of the PACAP gene in the dorsal pallium, ventral hypothalamus, and nuclei of cerebellum. PACAP mRNA signals were weak to moderate in the hypothalamic anterior preoptic area and were absent in the pituitary. Castration induced an increase in the expression of PACAP and PAC1 receptor mRNAs in the hypothalamic anterior preoptic area after 3 days. Replacement with testosterone prevented the castration-induced changes. These results provide a molecular basis for studying the physiological functions of PACAP in frog brain and suggest that PACAP may be involved in the feedback regulation of hypothalamic-pituitary-gonadal axis.

L3 ANSWER 3 OF 60 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1993:432491 BIOSIS
DOCUMENT NUMBER: PREV199396087116
TITLE: Two salmon neuropeptides encoded by one brain cDNA are structurally related to members of the glucagon superfamily.
AUTHOR(S): Parker, David B. [Reprint author]; Coe, Imogen R.; Dixon, Gordon H.; Sherwood, Nancy M.
CORPORATE SOURCE: Dep. Biol., P.O. Box 1700, Univ. Victoria, Victoria, BC V8W 2Y2, Canada
SOURCE: European Journal of Biochemistry, (1993) Vol. 215, No. 2, pp. 439-448.
CODEN: EJBCAI. ISSN: 0014-2956.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Sep 1993
Last Updated on STN: 23 Sep 1993

AB A cDNA that codes for two peptides in the glucagon superfamily has been isolated from sockeye salmon brain. The first peptide is related to **growth hormone-releasing hormone** (**GHRH**), which has high sequence similarity with PACAP-related peptide. The second peptide is structurally related to vasoactive intestinal peptide, which is also related to a newly identified peptide in mammals, pituitary adenylate-cyclase-activating polypeptide (PACAP). The salmon precursor contains 173 amino acids and has dibasic and monobasic enzyme-processing sites for cleavage of a 45-amino-acid **GHRH** -like peptide with a free C-terminus and a 38-amino-acid PACAP with an amidated C-terminus. The salmon **GHRH**-like peptide has 40% amino acid sequence identity with the human **GHRH** and 56% identity with human PACAP-related peptide. The 38-amino-acid salmon PACAP is highly conserved (89-92% identity) with only three or four **amino**

acid substitutions compared with the human, ovine and rat 38-amino-acid PACAP. Not previously reported for mammalian species, a short precursor coding for only one peptide exists in salmon in addition to the long precursor coding for two peptides. In the short precursor, the coding region for **GHRH** is deleted leaving the PACAP-coding region in a correct reading frame. This provides one possible control mechanism for an increased expression of one peptide (PACAP) without the concomitant increase in the other peptide (**GHRH**) as occurs in a double-peptide precursor. The importance of the 3' non-translated region of the salmon **GHRH**/PACAP precursor in the regulation of translation is suggested by its 70% nucleotide sequence identity to the 3' non-translated regions of the mammalian PACAP precursors. The structural organization of the salmon **GHRH**/PACAP precursor provides a possible evolutionary scheme for precursors that contain tandem peptides in the glucagon superfamily.

L3 ANSWER 4 OF 60 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1993:419010 BIOSIS
DOCUMENT NUMBER: PREV199345066635
TITLE: G-proteins and hormonal signalling in human pituitary tumors: Genetic mutations and functional alterations.
AUTHOR(S): Spada, Anna [Reprint author]; Vallar, Lucia; Faglia, Giovanni
CORPORATE SOURCE: Inst. Endocrine sci., Pad. Granelli, Ospedale Maggiore IRCCS, Via F. Sforza 35, 20122 Milano, Italy
SOURCE: Frontiers in Neuroendocrinology, (1993) Vol. 14, No. 3, pp. 214-232.
CODEN: FNEDA7. ISSN: 0091-3022.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Sep 1993
Last Updated on STN: 15 Sep 1993

L3 ANSWER 5 OF 60 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1992:480700 BIOSIS
DOCUMENT NUMBER: PREV199294112075; BA94:112075
TITLE: POTENT AGONISTS OF **GROWTH HORMONE-RELEASING HORMONE** II.
AUTHOR(S): ZARANDI M [Reprint author]; SERFOZO P; ZSIGO J; DEUTCH A H; JANAKY T; OLSEN D B; BAJUSZ S; SCHALLY A V
CORPORATE SOURCE: VETERANS AFFAIRS MED CENT, 1601 PERDIDO ST, NEW ORLEANS, LA 70146, USA
SOURCE: Peptide Research, (1992) Vol. 5, No. 4, pp. 190-193.
CODEN: PEREEO. ISSN: 1040-5704.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 27 Oct 1992
Last Updated on STN: 28 Oct 1992

AB Analogs of the 29-amino acid sequence of **growth hormone -releasing hormone** (GH-RH) with agmatine (Agm) or Lys-NH2 in position 29 have been synthesized by the solid-phase method, purified, and tested in vitro. Except for one peptide, all analogs contained desaminotyrosine (Dat) in position 1. All contained Nle27 in order to avoid oxidation of Met27. Some peptides contained one or more additional L- or D-**amino acid substitutions** in positions 2, 12, 15, 21, 27 and/or 28. Analogs [Dat1, Ala15, Nle27, Asn28]GH-RH(1-28)Agm (II, [Asn28]-Mz-2-51); [Dat1, Ala15, D-Lys21, Nle27, Asn28]GH-RH(1-28)Agm (III, MZ-3-125); and [Dat1, D-Asn8, Ala15, D-Lys21, Nle27, Asn28[GH-RH(1-28)Agm (IV, MZ-3-129) were 5.7, 2.8, and 3.9 times more potent in vitro, respectively, than GH-RH(1-29)NH2. However, if we compare the potencies of peptides II and III (analogs of the bovine sequence) with those of the analogs of human GH-RH (XII and XIII) [Dat1, Ala15, Nle27]GH-RH(1-128)Agm: [Dat1, Ala15, D-Lys21, Nle27]GH-RH(1-28)Agm, respectively, the GH-releasing potency was decreased by 50% and 33%, respectively, by the incorporation of Asn28. Our studies indicate that

Lys-NH2 at the C-terminus of GH-RH(1-29) and/or β-Ala, GABA (γ-amino-butyric acid), and Phe in position 15 are disadvantageous, but potent GH-RH analogs can result from the combination of agmatine in position 29 with other substitutions.

L3 ANSWER 6 OF 60 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1992:325329 BIOSIS
DOCUMENT NUMBER: PREV199294027170; BA94:27170
TITLE: POTENT AGONISTS OF **GROWTH HORMONE-RELEASING HORMONE** PART I.
AUTHOR(S): ZARANDI M [Reprint author]; SERFOZO P; ZSIGO J; BOKSER L; JANAKY T; OLSEN D B; BAJUSZ S; SCHALLY A V
CORPORATE SOURCE: VETERANS ADM MED CENT, 1601 PERDIDO ST, NEW ORLEANS, LA 70146, USA
SOURCE: International Journal of Peptide and Protein Research, (1992) Vol. 39, No. 3, pp. 211-217.
CODEN: IJPPC3. ISSN: 0367-8377.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 11 Jul 1992
Last Updated on STN: 11 Jul 1992

AB Analogs of the 29 amino acid sequence of **growth hormone-releasing hormone** (GH-RH) with agmatine (Agm) in position 29 have been synthesized by the solid phase method, purified, and tested in vitro and in vivo. The majority of the analogs contained desaminotyrosine (Dat) in position 1, but a few of them had Tyr1, or N-MeTyr1. Some peptides contained one or more additional L- or D-**amino acid substitutions** in positions 2, 12, 15, 21, 27, and/or 28. Compared to the natural sequence of GH-RH(1-29)NH2, [Dat1,Ala15]GH-RH(1-28)Agm (MZ-3-191) and [D-Ala2,Ala15]GH-RH(1-28)Agm (MZ-3-201) were 8.2 and 7.1 times more potent in vitro, respectively. These two peptides contained Met 27. Their Nle27 analogs, [Dat1,Ala15,Nle27]GH-RH(1-28)Agm(MZ-2-51), prepared previously (9), and [D-Ala2,Ala15,Nle28]GH-RH(1-28)Agm(MZ-3-195) showed relative in vitro potencies of 10.5 and 2.4, respectively. These data indicate that replacement of Met27 by Nle27 enhanced the GH-releasing activity of the analog when the molecule contained Dat1-Ala2 residues at the N-terminus, but peptides containing Tyr1-D-Ala2 in addition to Nle27 showed decreased potencies. Replacement of Ser28 with Asp in multi-substituted analogs of GH-RH(1-28)Agm resulted in a decrease in in vitro potencies compared to the parent compound. Thus, the Ser28-containing MZ-2-51, and [Dat1,Ala15,D-lys21,Nle27]GH-RH(1-28)Agm, its Asp28 homolog (MZ-3-149), possessed relative activities of 10.5 and 5.6, respectively. In vivo after the iv injection, the analogs [Dat1,Ala15,Nle27,Asp28]GH-RH(1-28)Agm (MZ-3-149), [Dat1,Ala15]GH-RH(1-28)Agm, (Mz-3-191) and [D-Ala2,Ala15]GH-RH(1-28)Agm (MZ-3-201) showed a potency equivalent to 7.6, 4.9 and 3.3 times that of GH-RH(1-29)NH2, respectively, at 5 min and 20.3, 4.3 and 1.7 times higher, respectively, at 15 min. After sc administration, analogs MZ-3-149, MZ-3-191, and MZ-3-201 were shown to be 63.7, 55.2 and 56.8 times more potent than the parent hormone at 15 min and 57.6, 60.6, and 42.6 times more active, respectively, at 30 min. In addition, MZ-3-149 had prolonged GH-releasing activity as compared to the standard, and proved to be more potent than MZ-2-51, the most active member of our previous series (8,9). Our studies indicate that very potent GH-RH analogs can result from the combination of agmatine in position 29 with other substitutions.

L3 ANSWER 7 OF 60 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1991:112764 BIOSIS
DOCUMENT NUMBER: PREV199191060154; BA91:60154
TITLE: SYNTHESIS AND IN-VITRO AND IN-VIVO ACTIVITY OF ANALOGS OF **GROWTH HORMONE-RELEASING HORMONE** GH-RH WITH CARBOXYL-TERMINAL AGMATINE.
AUTHOR(S): ZARANDI M [Reprint author]; CSERNUS V; BOKSER L; BAJUSZ S; GROOT K; SCHALLY A V
CORPORATE SOURCE: VETERANS ADM MED CENTER, 1601 PERDIDO ST, NEW ORLEANS, LA

70146, USA
SOURCE: International Journal of Peptide and Protein Research, (1990) Vol. 36, No. 6, pp. 499-505.
CODEN: IJPPC3. ISSN: 0367-8377.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 27 Feb 1991
Last Updated on STN: 28 Feb 1991

AB In the search for more active analogs of human **growth hormone-releasing hormone** (GH-RH), 37 new compounds were synthesized by solid phase methodology, purified, and tested biologically. Most of the analogs contained a sequence of 27 amino acids and N-terminal desaminotyrosine (Dat) and C-terminal agmatine (Agm), which are not amino acids. In addition to Dat in position 1 and Agm in position 29, the majority of the analogs had Ala15 and Nle27 substitutions and one or more additional L- or D-amino acid modifications. [Dat1, Ala15, Nle27]GH-RH(1-28)Agm (MZ-2-51) was the most active analog. Its is vitro GH-releasing potency was 10.5 times higher than that of GH-RH(1-29)NH2 and in the i.v. in vivo assay, MZ-2-51 was 4-5 times more active than the standard. After s.c. administration to rats, MZ-2-51 showed an activity 34 times higher at 15 min and 179 times greater at 30 min than GH-RH(1-29)NH2 and also displayed a prolonged activity. D-Tyr10,D-Lys12, and D-Lys21 homologs of MZ-2-51 also showed enhanced activities. Thus, [Dat1, D-Tyr10, Ala15, Nle27]GH-RH(1-28)Agm (MZ-2-159), [Dat1, D-Lys12, Ala15, Nle27]GH-RH(1-28)AGM (MZ-2-57], and [Dat1, Ala15, D-Lys21, Nle27]GH-RH(1-28)Agm (MZ-2-75) were 4-6 times more active in vitro than GH-RH(1-29)NH2. In vivo, after i.v. administration, analog MZ-2-75 was equipotent and analogs MZ-2-159 and MZ-2-57 about twice as potent as the standard. After s.c. administration, the potencies of MZ-2-57 and MZ-2-75 were 10-14 times higher than the standard at 15 min and 45-89 times greater when determined at 30 min. Most of the analogs containing two or more D-**amino acid substitutions** were less active than GH-RH(1-29)NH2 or inactive. Our studies indicate that very potent GH-RH analogs can result from the combination of agmatine in position 29 with other substitutions.

L3 ANSWER 8 OF 60 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1989:288928 BIOSIS
DOCUMENT NUMBER: PREV198988014272; BA88:14272
TITLE: DIPEPTIDYLPEPTIDASE IV AND TRYPSIN-LIKE ENZYMATIC DEGRADATION OF HUMAN **GROWTH HORMONE-RELEASING HORMONE** IN PLASMA.
AUTHOR(S): FROHMAN L A [Reprint author]; DOWNS T R; HEIMER E P; FELIX A M
CORPORATE SOURCE: DIV ENDOCRINOL METABOLISM, 231 BETHESDA AVE, ML NO 547, UNIV CINCINNATI COLL MED, CINCINNATI, OHIO 45267, USA
SOURCE: Journal of Clinical Investigation, (1989) Vol. 83, No. 5, pp. 1533-1540.
CODEN: JCINAO. ISSN: 0021-9738.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 20 Jun 1989
Last Updated on STN: 20 Jun 1989

AB The plasma enzyme responsible for primary proteolytic cleavage of **growth hormone-releasing hormone** (GRH) at the 2-3 amino acid bond was characterized. Native GRH[GRH(1-44)-NH2 and GRH(1-40)-OH], and COOH-terminally shortened fragments [GRH(1-32)-NH2 and GNRH(1-29)-NH2] were rapidly cleaved, while GRH(2-32)-NH2 was not degraded at this site. Moreover, degradation to GRH(3-44)-NH2 was unaffected by an aminopeptidase inhibitor, indicating that this metabolite was generated from a single step cleavage by a dipeptidylpeptidase (DPP) rather than sequential aminopeptidase cleavages. Conversion to GRH(3-44)-NH2 was blocked by diprotein A, a DPP type IV (DPP IV) competitive inhibitor. D-**Amino acid substitution** at either position 1 or 2 also prevented hydrolysis,

characteristic of DPP IV. Analysis of endogenous plasma GRH immunoreactivity from a human GRH transgenic pig revealed that the major peak coeluted with GRH(3-44)-NH2. Native GRH exhibited trypsin-like degradation at the 11-12 position but cleavage at the 12-13 site occurred only with GRH(1-32)-NH2 and GRH(1-29)-NH2. Formation of these metabolites was independent of prior DPP IV hydrolysis but was greatly reduced by trypsin inhibitors. Evaluation of plasma stability of potential GRH super analogues, designed to resist degradation by these enzymes, confirmed that GRH degradation in plasma occurs primarily by DPP IV, and to a lesser extent by trypsin-like enzyme(s).

L3 ANSWER 9 OF 60 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1987:129272 BIOSIS
DOCUMENT NUMBER: PREV198783068333; BA83:68333
TITLE: THE EFFECT OF INTRAVENOUS SUBCUTANEOUS AND INTRANASAL GH-RH ANALOG NORLEUCINE-27 GH-RH-1-29-AMINE ON GROWTH HORMONE SECRETION IN NORMAL MEN DOSE-RESPONSE RELATIONSHIPS.
AUTHOR(S): VANCE M L [Reprint author]; EVANS W S; KAISER D L; BURKE R L; RIVIER J; VALE W; THORNER M O
CORPORATE SOURCE: BOX 511, UNIV VIRGINIA MED CENT, CHARLOTTESVILLE, VA 22908, USA
SOURCE: Clinical Pharmacology and Therapeutics, (1986) Vol. 40, No. 6, pp. 627-633.
CODEN: CLPTAT. ISSN: 0009-9236.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 7 Mar 1987
Last Updated on STN: 7 Mar 1987

AB A 29 amino acid analog of **growth hormone releasing hormone** (GH-RH)-40 was given intravenously, subcutaneously, and intranasally to normal men to determine its effectiveness in stimulating growth hormone (GH) release. The GH-RH analog, [Nle27]GH-RH(1-29)-NH2, is an amidated 29 amino acid peptide that has one **amino acid substitution** at position 27. This peptide stimulates GH secretion when given by the intravenous, subcutaneous, and intranasal routes without adverse effect. The degree of GH stimulation was variable among subjects and the greatest amount of stimulation occurred with the highest doses. GH stimulation occurred in a dose-responsive manner after all three routes of administration. A tenfold higher subcutaneous dose was required to stimulate a comparable amount of GH secretion as compared with intravenous administration, and a thirtyfold higher intranasal than intravenous dose was required to stimulate approximately one fifth the amount of GH release. For comparison, one dose of GH-RH-40, 1 μg/kg, was administered intravenously. GH secretion after 1 μg/kg, GH-RH-40 and 1 μg/kg Nle27 GH-RH was comparable between the two groups of subjects. Stimulation of GH secretion by Nle27 GH-RH occurred within 5 minutes of intravenous and within 10 minutes of subcutaneous and intranasal administration; peak GH levels were observed within 30 minutes. GH levels declined and returned to near baseline levels 2 hours after administration of the analog. Since GH-RH-40 has been demonstrated to be effective in stimulating GH release and promoting acceleration of linear growth in GH-deficient children, it is likely that a shorter peptide with full biologic activity such as Nle27 GH-RH may also be effective in the treatment of some children with GH deficiency.

L3 ANSWER 10 OF 60 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:242357 CAPLUS
DOCUMENT NUMBER: 137:261156
TITLE: Molecular analysis of the **growth hormone releasing hormone** receptor gene (**GHRH**-R) in isolated growth hormone deficiency: Identification of a likely etiological mutation in the signal peptide
AUTHOR(S): Lessi, Monica; Giordano, Mara; Paracchini, Roberta; Petri, Antonella; Federico, Giovanni; Wasniewska,

Malgorzata; Pasquino, Anna Maria; Aimaretti, Gianluca; Bona, Gianni; Momigliano-Richiardi, Patricia
CORPORATE SOURCE: Cattedra di Genetica Umana, Universita del Piemonte Orientale "Amedeo Avogadro", Novara, 28100, Italy
SOURCE: Journal of Endocrine Genetics (2001), 2(4), 215-228
CODEN: JEGEF6; ISSN: 1565-012X
PUBLISHER: Freund
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The coding sequence, the intron-exon boundaries and the proximal promoter of the **growth hormone releasing hormone** receptor gene (**GHRH**-R) were screened for sequence variations in 22 unrelated Italian patients with isolated growth hormone deficiency (IGHD). Six single nucleotide variations were detected in the 5' flanking region, five in the intronic sequences and five leading to **amino acid substitutions**. All the variations had comparable frequencies in the patients and in controls except for T29C, leading to a Val10Gly substitution in the signal peptide, which was present in the heterozygous state in one patient and was never detected in 1226 control chromosomes. Gly has different physio-chemical properties from Val and Ile commonly present in the homologous position in closely related species, and it is never found in the corresponding position of eukaryotic signal peptides. Thus this missense substitution might represent a new IGHD etiol. dominant mutation acting through a pathophysiol. mechanism involving the signal peptide.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l3 and (bovine or human or cattle or cow? or ovine)
L9 53 L3 AND (BOVINE OR HUMAN OR CATTLE OR COW? OR OVINE)

=> display
ENTER (L9), L# OR ?:l9
ENTER ANSWER NUMBER OR RANGE (1):1-10
ENTER DISPLAY FORMAT (FILEDEFAULT):ibib abs

L9 ANSWER 1 OF 53 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:152522 BIOSIS
DOCUMENT NUMBER: PREV200100152522
TITLE: Molecular cloning of **growth hormone-releasing hormone**/pituitary adenylyl cyclase-activating polypeptide in the frog Xenopus laevis: Brain distribution and regulation after castration.
AUTHOR(S): Hu, Zhongting; Lelievre, Vincent; Tam, Jimmy; Cheng, Jennifer W.; Fuenzalida, Gabriel; Zhou, Xinrong; Waschek, James A. [Reprint author]
CORPORATE SOURCE: Department of Psychiatry, University of California, 760 Westwood Plaza, 68-225 NPI, Los Angeles, CA, 90024, USA jwaschek@mednet.ucla.edu
SOURCE: Endocrinology, (September, 2000) Vol. 141, No. 9, pp. 3366-3376. print.
CODEN: ENDOAO. ISSN: 0013-7227.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Mar 2001
Last Updated on STN: 15 Feb 2002
AB Pituitary adenylyl cyclase-activating peptide (PACAP) appears to regulate several neuroendocrine functions in the frog, but its messenger RNA (mRNA) structure and brain distribution are unknown. To understand the potential role of PACAP in the male frog hypothalamic-pituitary-gonadal axis, we cloned the frog Xenopus laevis PACAP mRNA and determined its distribution in the brain. We then analyzed the castration-induced alterations of mRNA expression for PACAP and its selective type I receptor (PAC1) in the hypothalamic anterior preoptic area, a region known to regulate reproductive function. The PACAP mRNA encodes a peptide precursor predicted to give rise to both GH-releasing hormone and PACAP. The

deduced peptide sequence of PACAP-38 was nearly identical to that of **human** PACAP with one **amino acid substitution**. Abundant PACAP mRNA was detected in the brain, but not several other tissues, including the testis. In situ hybridization revealed strong expression of the PACAP gene in the dorsal pallium, ventral hypothalamus, and nuclei of cerebellum. PACAP mRNA signals were weak to moderate in the hypothalamic anterior preoptic area and were absent in the pituitary. Castration induced an increase in the expression of PACAP and PAC1 receptor mRNAs in the hypothalamic anterior preoptic area after 3 days. Replacement with testosterone prevented the castration-induced changes. These results provide a molecular basis for studying the physiological functions of PACAP in frog brain and suggest that PACAP may be involved in the feedback regulation of hypothalamic-pituitary-gonadal axis.

L9 ANSWER 2 OF 53 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1993:432491 BIOSIS
DOCUMENT NUMBER: PREV199396087116
TITLE: Two salmon neuropeptides encoded by one brain cDNA are structurally related to members of the glucagon superfamily.
AUTHOR(S): Parker, David B. [Reprint author]; Coe, Imogen R.; Dixon, Gordon H.; Sherwood, Nancy M.
CORPORATE SOURCE: Dep. Biol., P.O. Box 1700, Univ. Victoria, Victoria, BC V8W 2Y2, Canada
SOURCE: European Journal of Biochemistry, (1993) Vol. 215, No. 2, pp. 439-448.
CODEN: EJBCAI. ISSN: 0014-2956.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Sep 1993
Last Updated on STN: 23 Sep 1993

AB A cDNA that codes for two peptides in the glucagon superfamily has been isolated from sockeye salmon brain. The first peptide is related to **growth hormone-releasing hormone** (**GHRH**), which has high sequence similarity with PACAP-related peptide. The second peptide is structurally related to vasoactive intestinal peptide, which is also related to a newly identified peptide in mammals, pituitary adenylate-cyclase-activating polypeptide (PACAP). The salmon precursor contains 173 amino acids and has dibasic and monobasic enzyme-processing sites for cleavage of a 45-amino-acid **GHRH** -like peptide with a free C-terminus and a 38-amino-acid PACAP with an amidated C-terminus. The salmon **GHRH**-like peptide has 40% amino acid sequence identity with the **human GHRH** and 56% identity with **human** PACAP-related peptide. The 38-amino-acid salmon PACAP is highly conserved (89-92% identity) with only three or four **amino acid substitutions** compared with the **human, ovine** and rat 38-amino-acid PACAP. Not previously reported for mammalian species, a short precursor coding for only one peptide exists in salmon in addition to the long precursor coding for two peptides. In the short precursor, the coding region for **GHRH** is deleted leaving the PACAP-coding region in a correct reading frame. This provides one possible control mechanism for an increased expression of one peptide (PACAP) without the concomitant increase in the other peptide (**GHRH**) as occurs in a double-peptide precursor. The importance of the 3' non-translated region of the salmon **GHRH**/PACAP precursor in the regulation of translation is suggested by its 70% nucleotide sequence identity to the 3' non-translated regions of the mammalian PACAP precursors. The structural organization of the salmon **GHRH**/PACAP precursor provides a possible evolutionary scheme for precursors that contain tandem peptides in the glucagon superfamily.

L9 ANSWER 3 OF 53 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1993:419010 BIOSIS
DOCUMENT NUMBER: PREV199345066635
TITLE: G-proteins and hormonal signalling in **human**

pituitary tumors: Genetic mutations and functional alterations.
AUTHOR(S): Spada, Anna [Reprint author]; Vallar, Lucia; Faglia, Giovanni
CORPORATE SOURCE: Inst. Endocrine sci., Pad. Granelli, Ospedale Maggiore IRCCS, Via F. Sforza 35, 20122 Milano, Italy
SOURCE: Frontiers in Neuroendocrinology, (1993) Vol. 14, No. 3, pp. 214-232.
CODEN: FNEDA7. ISSN: 0091-3022.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Sep 1993
Last Updated on STN: 15 Sep 1993

L9 ANSWER 4 OF 53 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1992:480700 BIOSIS
DOCUMENT NUMBER: PREV199294112075; BA94:112075
TITLE: POTENT AGONISTS OF **GROWTH HORMONE-RELEASING HORMONE** II.
AUTHOR(S): ZARANDI M [Reprint author]; SERFOZO P; ZSIGO J; DEUTCH A H; JANAKY T; OLSEN D B; BAJUSZ S; SCHALLY A V
CORPORATE SOURCE: VETERANS AFFAIRS MED CENT, 1601 PERDIDO ST, NEW ORLEANS, LA 70146, USA
SOURCE: Peptide Research, (1992) Vol. 5, No. 4, pp. 190-193.
CODEN: PEREEO. ISSN: 1040-5704.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 27 Oct 1992
Last Updated on STN: 28 Oct 1992
AB Analogs of the 29-amino acid sequence of **growth hormone -releasing hormone** (GH-RH) with agmatine (Agm) or Lys-NH2 in position 29 have been synthesized by the solid-phase method, purified, and tested in vitro. Except for one peptide, all analogs contained desaminotyrosine (Dat) in position 1. All contained Nle27 in order to avoid oxidation of Met27. Some peptides contained one or more additional L- or D-**amino acid substitutions** in positions 2, 12, 15, 21, 27 and/or 28. Analogs [Dat1, Ala15, Nle27, Asn28]GH-RH(1-28)Agm (II, [Asn28]-Mz-2-51); [Dat1, Ala15, D-Lys21, Nle27, Asn28]GH-RH(1-28)Agm (III, MZ-3-125); and [Dat1, D-Asn8, Ala15, D-Lys21, Nle27, Asn28[GH-RH(1-28)Agm (IV, MZ-3-129) were 5.7, 2.8, and 3.9 times more potent in vitro, respectively, than GH-RH(1-29)NH2. However, if we compare the potencies of peptides II and III (analogs of the **bovine** sequence) with those of the analogs of **human** GH-RH (XII and XIII) [Dat1, Ala15, Nle27]GH-RH(1-128)Agm: [Dat1, Ala15, D-Lys21, Nle27]GH-RH(1-28)Agm, respectively, the GH-releasing potency was decreased by 50% and 33%, respectively, by the incorporation of Asn28. Our studies indicate that Lys-NH2 at the C-terminus of GH-RH(1-29) and/or β-Ala, GABA (γ-amino-butyric acid), and Phe in position 15 are disadvantageous, but potent GH-RH analogs can result from the combination of agmatine in position 29 with other substitutions.

L9 ANSWER 5 OF 53 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1992:325329 BIOSIS
DOCUMENT NUMBER: PREV199294027170; BA94:27170
TITLE: POTENT AGONISTS OF **GROWTH HORMONE-RELEASING HORMONE** PART I.
AUTHOR(S): ZARANDI M [Reprint author]; SERFOZO P; ZSIGO J; BOKSER L; JANAKY T; OLSEN D B; BAJUSZ S; SCHALLY A V
CORPORATE SOURCE: VETERANS ADM MED CENT, 1601 PERDIDO ST, NEW ORLEANS, LA 70146, USA
SOURCE: International Journal of Peptide and Protein Research, (1992) Vol. 39, No. 3, pp. 211-217.
CODEN: IJPPC3. ISSN: 0367-8377.
DOCUMENT TYPE: Article
FILE SEGMENT: BA

LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 11 Jul 1992
Last Updated on STN: 11 Jul 1992

AB Analogs of the 29 amino acid sequence of **growth hormone -releasing hormone** (GH-RH) with agmatine (Agm) in position 29 have been synthesized by the solid phase method, purified, and tested in vitro and in vivo. The majority of the analogs contained desaminotyrosine (Dat) in position 1, but a few of them had Tyr1, or N-MeTyr1. Some peptides contained one or more additional L- or D-**amino acid substitutions** in positions 2, 12, 15, 21, 27, and/or 28. Compared to the natural sequence of GH-RH(1-29)NH2, [Dat1,Ala15]GH-RH(1-28)Agm (MZ-3-191) and [D-Ala2,Ala15]GH-RH(1-28)Agm (MZ-3-201) were 8.2 and 7.1 times more potent in vitro, respectively. These two peptides contained Met 27. Their Nle27 analogs, [Dat1,Ala15,Nle27]GH-RH(1-28)Agm(MZ-2-51), prepared previously (9), and [D-Ala2,Ala15,Nle28]GH-RH(1-28)Agm(MZ-3-195) showed relative in vitro potencies of 10.5 and 2.4, respectively. These data indicate that replacement of Met27 by Nle27 enhanced the GH-releasing activity of the analog when the molecule contained Dat1-Ala2 residues at the N-terminus, but peptides containing Tyr1-D-Ala2 in addition to Nle27 showed decreased potencies. Replacement of Ser28 with Asp in multi-substituted analogs of GH-RH(1-28)Agm resulted in a decrease in in vitro potencies compared to the parent compound. Thus, the Ser28-containing MZ-2-51, and [Dat1,Ala15,D-lys21,Nle27]GH-RH(1-28)Agm, its Asp28 homolog (MZ-3-149), possessed relative activities of 10.5 and 5.6, respectively. In vivo after the iv injection, the analogs [Dat1,Ala15,Nle27,Asp28]GH-RH(1-28)Agm (MZ-3-149), [Dat1,Ala15]GH-RH(1-28)Agm, (Mz-3-191) and [D-Ala2,Ala15]GH-RH(1-28)Agm (MZ-3-201) showed a potency equivalent to 7.6, 4.9 and 3.3 times that of GH-RH(1-29)NH2, respectively, at 5 min and 20.3, 4.3 and 1.7 times higher, respectively, at 15 min. After sc administration, analogs MZ-3-149, MZ-3-191, and MZ-3-201 were shown to be 63.7, 55.2 and 56.8 times more potent than the parent hormone at 15 min and 57.6, 60.6, and 42.6 times more active, respectively, at 30 min. In addition, MZ-3-149 had prolonged GH-releasing activity as compared to the standard, and proved to be more potent than MZ-2-51, the most active member of our previous series (8,9). Our studies indicate that very potent GH-RH analogs can result from the combination of agmatine in position 29 with other substitutions.

L9 ANSWER 6 OF 53 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1991:112764 BIOSIS
DOCUMENT NUMBER: PREV199191060154; BA91:60154
TITLE: SYNTHESIS AND IN-VITRO AND IN-VIVO ACTIVITY OF ANALOGS OF **GROWTH HORMONE-RELEASING HORMONE** GH-RH WITH CARBOXYL-TERMINAL AGMATINE.
AUTHOR(S): ZARANDI M [Reprint author]; CSERNUS V; BOKSER L; BAJUSZ S; GROOT K; SCHALLY A V
CORPORATE SOURCE: VETERANS ADM MED CENTER, 1601 PERDIDO ST, NEW ORLEANS, LA 70146, USA
SOURCE: International Journal of Peptide and Protein Research, (1990) Vol. 36, No. 6, pp. 499-505.
CODEN: IJPPC3. ISSN: 0367-8377.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 27 Feb 1991
Last Updated on STN: 28 Feb 1991

AB In the search for more active analogs of **human growth hormone-releasing hormone** (GH-RH), 37 new compounds were synthesized by solid phase methodology, purified, and tested biologically. Most of the analogs contained a sequence of 27 amino acids and N-terminal desaminotyrosine (Dat) and C-terminal agmatine (Agm), which are not amino acids. In addition to Dat in position 1 and Agm in position 29, the majority of the analogs had Ala15 and Nle27 substitutions and one or more additional L- or D-amino acid modifications. [Dat1, Ala15, Nle27]GH-RH(1-28)Agm (MZ-2-51) was the most active analog. Its is vitro GH-releasing potency was 10.5 times higher than that of GH-RH(1-29)NH2 and

in the i.v. in vivo assay, MZ-2-51 was 4-5 times more active than the standard. After s.c. administration to rats, MZ-2-51 showed an activity 34 times higher at 15 min and 179 times greater at 30 min than GH-RH(1-29)NH2 and also displayed a prolonged activity. D-Tyr10,D-Lys12, and D-Lys21 homologs of MZ-2-51 also showed enhanced activities. Thus, [Dat1, D-Tyr10, Ala15, Nle27]GH-RH(1-28)Agm (MZ-2-159), [Dat1, D-Lys12, Ala15, Nle27]GH-RH(1-28)AGM (MZ-2-57], and [Dat1, Ala15, D-Lys21, Nle27]GH-RH(1-28)Agm (MZ-2-75) were 4-6 times more active in vitro than GH-RH(1-29)NH2. In vivo, after i.v. administration, analog MZ-2-75 was equipotent and analogs MZ-2-159 and MZ-2-57 about twice as potent as the standard. After s.c. administration, the potencies of MZ-2-57 and MZ-2-75 were 10-14 times higher than the standard at 15 min and 45-89 times greater when determined at 30 min. Most of the analogs containing two or more D-**amino acid substitutions** were less active than GH-RH(1-29)NH2 or inactive. Our studies indicate that very potent GH-RH analogs can result from the combination of agmatine in position 29 with other substitutions.

L9 ANSWER 7 OF 53 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1989:288928 BIOSIS
DOCUMENT NUMBER: PREV198988014272; BA88:14272
TITLE: DIPEPTIDYLPEPTIDASE IV AND TRYPSIN-LIKE ENZYMATIC DEGRADATION OF **HUMAN GROWTH HORMONE-RELEASING HORMONE** IN PLASMA.
AUTHOR(S): FROHMAN L A [Reprint author]; DOWNS T R; HEIMER E P; FELIX A M
CORPORATE SOURCE: DIV ENDOCRINOL METABOLISM, 231 BETHESDA AVE, ML NO 547, UNIV CINCINNATI COLL MED, CINCINNATI, OHIO 45267, USA
SOURCE: Journal of Clinical Investigation, (1989) Vol. 83, No. 5, pp. 1533-1540.
CODEN: JCINAO. ISSN: 0021-9738.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 20 Jun 1989
Last Updated on STN: 20 Jun 1989

AB The plasma enzyme responsible for primary proteolytic cleavage of **growth hormone-releasing hormone** (GRH) at the 2-3 amino acid bond was characterized. Native GRH[GRH(1-44)-NH2 and GRH(1-40)-OH], and COOH-terminally shortened fragments [GRH(1-32)-NH2 and GNRH(1-29)-NH2] were rapidly cleaved, while GRH(2-32)-NH2 was not degraded at this site. Moreover, degradation to GRH(3-44)-NH2 was unaffected by an aminopeptidase inhibitor, indicating that this metabolite was generated from a single step cleavage by a dipeptidylpeptidase (DPP) rather than sequential aminopeptidase cleavages. Conversion to GRH(3-44)-NH2 was blocked by diprotein A, a DPP type IV (DPP IV) competitive inhibitor. D-**Amino acid substitution** at either position 1 or 2 also prevented hydrolysis, characteristic of DPP IV. Analysis of endogenous plasma GRH immunoreactivity from a **human** GRH transgenic pig revealed that the major peak coeluted with GRH(3-44)-NH2. Native GRH exhibited trypsin-like degradation at the 11-12 position but cleavage at the 12-13 site occurred only with GRH(1-32)-NH2 and GRH(1-29)-NH2. Formation of these metabolites was independent of prior DPP IV hydrolysis but was greatly reduced by trypsin inhibitors. Evaluation of plasma stability of potential GRH super analogues, designed to resist degradation by these enzymes, confirmed that GRH degradation in plasma occurs primarily by DPP IV, and to a lesser extent by trypsin-like enzyme(s).

L9 ANSWER 8 OF 53 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1987:129272 BIOSIS
DOCUMENT NUMBER: PREV198783068333; BA83:68333
TITLE: THE EFFECT OF INTRAVENOUS SUBCUTANEOUS AND INTRANASAL GH-RH ANALOG NORLEUCINE-27 GH-RH-1-29-AMINE ON GROWTH HORMONE SECRETION IN NORMAL MEN DOSE-RESPONSE RELATIONSHIPS.
AUTHOR(S): VANCE M L [Reprint author]; EVANS W S; KAISER D L; BURKE R

L; RIVIER J; VALE W; THORNER M O
CORPORATE SOURCE: BOX 511, UNIV VIRGINIA MED CENT, CHARLOTTESVILLE, VA 22908, USA
SOURCE: Clinical Pharmacology and Therapeutics, (1986) Vol. 40, No. 6, pp. 627-633.
CODEN: CLPTAT. ISSN: 0009-9236.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 7 Mar 1987
Last Updated on STN: 7 Mar 1987

AB A 29 amino acid analog of **growth hormone releasing hormone** (GH-RH)-40 was given intravenously, subcutaneously, and intranasally to normal men to determine its effectiveness in stimulating growth hormone (GH) release. The GH-RH analog, [Nle27]GH-RH(1-29)-NH2, is an amidated 29 amino acid peptide that has one **amino acid substitution** at position 27. This peptide stimulates GH secretion when given by the intravenous, subcutaneous, and intranasal routes without adverse effect. The degree of GH stimulation was variable among subjects and the greatest amount of stimulation occurred with the highest doses. GH stimulation occurred in a dose-responsive manner after all three routes of administration. A tenfold higher subcutaneous dose was required to stimulate a comparable amount of GH secretion as compared with intravenous administration, and a thirtyfold higher intranasal than intravenous dose was required to stimulate approximately one fifth the amount of GH release. For comparison, one dose of GH-RH-40, 1 μg/kg, was administered intravenously. GH secretion after 1 μg/kg, GH-RH-40 and 1 μg/kg Nle27 GH-RH was comparable between the two groups of subjects. Stimulation of GH secretion by Nle27 GH-RH occurred within 5 minutes of intravenous and within 10 minutes of subcutaneous and intranasal administration; peak GH levels were observed within 30 minutes. GH levels declined and returned to near baseline levels 2 hours after administration of the analog. Since GH-RH-40 has been demonstrated to be effective in stimulating GH release and promoting acceleration of linear growth in GH-deficient children, it is likely that a shorter peptide with full biologic activity such as Nle27 GH-RH may also be effective in the treatment of some children with GH deficiency.

L9 ANSWER 9 OF 53 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:242357 CAPLUS
DOCUMENT NUMBER: 137:261156
TITLE: Molecular analysis of the **growth hormone releasing hormone** receptor gene (**GHRH**-R) in isolated growth hormone deficiency: Identification of a likely etiological mutation in the signal peptide
AUTHOR(S): Lessi, Monica; Giordano, Mara; Paracchini, Roberta; Petri, Antonella; Federico, Giovanni; Wasniewska, Malgorzata; Pasquino, Anna Maria; Aimaretti, Gianluca; Bona, Gianni; Momigliano-Richiardi, Patricia
CORPORATE SOURCE: Cattedra di Genetica Umana, Universita del Piemonte Orientale "Amedeo Avogadro", Novara, 28100, Italy
SOURCE: Journal of Endocrine Genetics (2001), 2(4), 215-228
CODEN: JEGEF6; ISSN: 1565-012X
PUBLISHER: Freund
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The coding sequence, the intron-exon boundaries and the proximal promoter of the **growth hormone releasing hormone** receptor gene (**GHRH**-R) were screened for sequence variations in 22 unrelated Italian patients with isolated growth hormone deficiency (IGHD). Six single nucleotide variations were detected in the 5' flanking region, five in the intronic sequences and five leading to **amino acid substitutions**. All the variations had comparable frequencies in the patients and in controls except for T29C, leading to a Val10Gly substitution in the signal peptide,

which was present in the heterozygous state in one patient and was never detected in 1226 control chromosomes. Gly has different physio-chemical properties from Val and Ile commonly present in the homologous position in closely related species, and it is never found in the corresponding position of eukaryotic signal peptides. Thus this missense substitution might represent a new IGHD etiol. dominant mutation acting through a pathophysiol. mechanism involving the signal peptide.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 53 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:603845 CAPLUS
DOCUMENT NUMBER: 133:293896
TITLE: Molecular cloning of **growth hormone -releasing hormone**/pituitary adenylyl cyclase-activating polypeptide in the frog Xenopus laevis: brain distribution and regulation after castration
AUTHOR(S): Hu, Zhongting; Lelievre, Vincent; Tam, Jimmy; Cheng, Jennifer W.; Fuenzalida, Gabriel; Zhou, Xinrong; Waschek, James A.
CORPORATE SOURCE: Department of Psychiatry, Mental Retardation Research Center, University of California School of Medicine, Los Angeles, CA, 90024-1759, USA
SOURCE: Endocrinology (2000), 141(9), 3366-3376
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To understand the potential role of PACAP in the male frog hypothalamic-pituitary-gonadal axis, we cloned the frog X. laevis PACAP mRNA and determined its distribution in the brain. We then analyzed the castration-induced alterations of mRNA expression for PACAP and its selective type I receptor (PAC1) in the hypothalamic anterior preoptic area, a region known to regulate reproductive function. The PACAP mRNA encodes a peptide precursor predicted to give rise to both GH-releasing hormone and PACAP. The deduced peptide sequence of PACAP-38 was nearly identical to that of **human** PACAP with 1 **amino acid substitution**. Abundant PACAP mRNA was detected in the brain, but not several other tissues, including the testis. In situ hybridization revealed strong expression of the PACAP gene in the dorsal pallium, ventral hypothalamus, and nuclei of cerebellum. PACAP mRNA signals were weak to moderate in the hypothalamic anterior preoptic area and were absent in the pituitary. Castration induced an increase in the expression of PACAP and PAC1 receptor mRNAs in the hypothalamic anterior preoptic area after 3 days. Replacement with testosterone prevented the castration-induced changes. These results provide a mol. basis for studying the physiol. functions of PACAP in frog brain and suggest that PACAP may be involved in the feedback regulation of hypothalamic-pituitary-gonadal axis.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> display l9
YOU HAVE REQUESTED DATA FROM FILE 'BIOSIS, CAPLUS, MEDLINE, SCISEARCH, EMBASE' - CONTINUE? (Y)/N:y

ENTER ANSWER NUMBER OR RANGE (1):11-20
ENTER DISPLAY FORMAT (FILEDEFAULT):ti abs

L9 ANSWER 11 OF 53 CAPLUS COPYRIGHT 2005 ACS on STN
TI Modification of polypeptide drugs to increase electrotransport flux
AB Methods of modifying polypeptide drugs in order to enhance their transdermal electrotransport flux are provided. The polypeptide is modified by substituting a histidine residue (His) for one or more glutamine (Gln), threonine (Thr) and/or asparagine (Asn) residue(s). The His for Gln substitution is particularly preferred from the standpoint of retaining biol. activity of the parent polypeptide. Compns. containing the modified polypeptide, which are useful for transdermal electrotransport delivery, are also provided. Analogs, e.g. a PTH analog, showed improved electrotransport plasma levels. A schematic drawing of an electrotransport drug delivery device is included.

L9 ANSWER 12 OF 53 CAPLUS COPYRIGHT 2005 ACS on STN
TI Two salmon neuropeptides encoded by one brain cDNA are structurally related to members of the glucagon superfamily
AB A cDNA that codes for two peptides in the glucagon superfamily has been isolated from sockeye salmon brain. The first peptide is related to **growth hormone-releasing hormone** (**GHRH**), which has high sequence similarity with PACAP-related peptide. The second peptide is structurally related to vasoactive intestinal peptide, which is also related to a newly identified peptide in mammals, pituitary adenylate-cyclase-activating polypeptide (PACAP). The salmon precursor contains 173 amino acids and has dibasic and monobasic enzyme-processing sites for cleavage of a 45-amino-acid **GHRH** -like peptide with a free C-terminus and a 38-amino-acid PACAP with an amidated C-terminus. The salmon **GHRH**-like peptide has 40% amino acid sequence identity with the **human GHRH** and 56% identity with **human** PACAP-related peptide. The 38-amino-acid salmon PACAP is highly conserved (89-92% identity(with only three or four **amino acid substitutions** compared with the **human, ovine** and rat 38-amino-acid PACAP. Not previously reported for mammalian species, a short precursor coding for only one peptide exists in salmon in addition to the long precursor coding for two peptides. In the short precursor, the coding region for **GHRH** is deleted leaving the PACAP-coding region in a correct reading frame. This provides one possible control mechanism for an increased expression of one peptide (PACAP) without the concomitant increase in the other peptide (**GHRH**) as occurs in a double-peptide precursor. The importance of the 3' non-translated region of the salmon **GHRH**/PACAP precursor in the regulation of translation is suggested by its 70% nucleotide sequence identity to the 3' non-translated regions of the mammalian PACAP precursors. The structural organization of the salmon **GHRH**/PACAP precursor provides a possible evolutionary scheme for precursors that contain tandem peptides in the glucagon superfamily.

L9 ANSWER 13 OF 53 CAPLUS COPYRIGHT 2005 ACS on STN
TI Potent agonists of **growth hormone-releasing hormone**. II
AB Analogs of the 29-amino acid sequence of **growth hormone -releasing hormone** (GH-RH) with agmatine (Agm) or Lys-NH2 in position 29 have been synthesized by the solid-phase method, purified, and tested in vitro. Except for one peptide, all analogs contained desaminotyrosine (Dat) in position 1. All contained Nle27 in

order to avoid oxidation of Met27. Some peptides contained one or more addnl. L- or D-**amino acid substitutions** in positions 2, 12, 15, 21, 27 and/or 28. Analogs [Dat1,Ala15,Nle27,Asn28]GH-RH(1-28)Agm (I), [Dat1,Ala15,D-Lys21,Nle27,Asn28]GH-RH(1-28)Agm (II), and [Dat1,D-Asn8,Ala15,D-Lys21,Nle27,Asn28]GH-RH(1-28)Agm were 5.7, 2.8, and 3.9 times more potent in vitro, resp., than GH-RH(1-29)NH2. However, comparison of the potencies of peptides I and II (analogs of the **bovine** sequence) with those of the analogs of **human** GH-RH, [Dat1,Ala15,Nle27]GH-RH(1-29)Agm and [Dat1,Ala15,D-Lys21,Nle27]GH-RH(1-28)Agm, resp., the GH-releasing potency was decreased by 50% and 33%, resp., by the incorporation of Asn28. The studies indicate that Lys-NH2 at the C-terminus of GH-RH(1-29) and/or β-Ala, GABA (γ-amino-butyric acid), and Phe in position 15 are disadvantageous, but potent GH-RH analogs can result from the combination of agmatine in position 29 with other substitutions.

L9 ANSWER 14 OF 53 CAPLUS COPYRIGHT 2005 ACS on STN
TI Synthesis and biological activities of analogs of hGH-RH with C-terminal agmatine
AB Some analogs of **human growth hormone-releasing hormone** (hGH-RH)(1-29)NH2 with a single D-**amino acid substitution** or replacement of Tyr1 by desamino-Tyr(Dat), Gly15 by Ala, and Arg29 by agmatine (4-guanidinobutylamine, Agm) have increased GH-releasing activities. Based on these earlier findings, the authors have synthesized a series of multiple replacement analogs of hGH-RH(1-29)NH2.

L9 ANSWER 15 OF 53 CAPLUS COPYRIGHT 2005 ACS on STN
TI Synthesis and in vitro and in vivo activity of analogs of **growth hormone-releasing hormone** (GH-RH) with C-terminal agmatine
AB In the search for more active analogs of **human growth hormone-releasing hormone** (GH-RH), 37 new compds. were synthesized by solid phase methodol., purified, and tested biol. Most of the analogs contained a sequence of 27 amino acids and N-terminal desaminotyrosine (Dat) and C-terminal agmatine (Agm), which are not amino acids. In addition to Dat in position 1 and Agm in position 29, the majority of the analogs had Ala15 and Nle27 substitutions and 1 or more addnl. L- or D-amino acid modifications. [Dat1, Ala15, Nle27]GH-RH(1-28)Agm (MZ-2-51) was the most active analog. Its in vitro GH-releasing potency was 10.5 times higher than that of GH-RH(1-29)NH2 and in the i.v. in vivo assay, MZ-2-51 was 4-5 times more active than the standard After s.c. administration to rats, MZ-2-51 showed an activity 34 times higher at 15 min and 179 times greater at 30 min than GH-RH(1-29)NH2 and also displayed a prolonged activity. D-Tyr10, D-Lys12, and D-Lys21 homologs of MZ-2-51 also showed enhanced activities. Thus, [Dat1, D-Tyr10, Ala15, Nle27]GH-RH(1-28)Agm (MZ-2-159), [Dat1, D-Lys12, Ala15, Nle27]GH-RH(1-28)AGM (MZ-2-57), and [Dat1, Ala15, D-Lys21, Nle27]GH-RH(1-28)Agm (MZ-2-75) were 4-6 times more active in vitro than GH-RH(1-29)NH2. In vivo, after i.v. administration, analog MZ-2-75 was equipotent and analogs MZ-2-159 and MZ-2-57 about twice as potent as the standard After s.c. administration, the potencies of MZ-2-57 and MZ-2-75 were 10-14 times higher than the standard at 15 min and 45-89 times greater when determined at 30 min. Most of the analogs containing 2 or more D-**amino acid substitutions** were less active than GH-RH(1-29)NH2 or inactive. Thus, very potent GH-RH analogs can result from the combination of agmatine in position 29 with other substitutions.

L9 ANSWER 16 OF 53 CAPLUS COPYRIGHT 2005 ACS on STN
TI Dipeptidylpeptidase IV and trypsin-like enzymic degradation of **human growth hormone-releasing hormone** in plasma
AB The **human** plasma enzyme responsible for primary proteolytic cleavage of **growth hormone-releasing hormone** (GRH) at the 2-3 amino acid bond was characterized. Native GRH [GRH(1-44)-NH2 and GRH(1-40)-OH], and C-terminally shortened fragments [GRH(1-32)-NH2 and GRH(1-29)-NH2] were rapidly cleaved, whereas

GRH(2-32)-NH2 was not degraded at this site. Moreover, degradation to GRH(3-44)-NH2 was unaffected by an aminopeptidase inhibitor, indicating that this metabolite was generated from a single step cleavage by a dipeptidylpeptidase (DPP) rather than sequential aminopeptidase cleavages. Conversion to GRH(3-44)-NH2 was blocked by diprotin A, a DPP type IV competitive inhibitor. D-**Amino acid substitution** at either position 1 or 2 also prevented hydrolysis, characteristic of DPP IV. Anal. of endogenous plasma GRH immunoreactivity from a **human** GRH transgenic pig revealed that the major peak coeluted with GRH(3-44)-NH2. Native GRH exhibited trypsin-like degradation at the 11-12 position but cleavage at the 12-13 site occurred only with GRH(1-32)-NH2 and GRH(1-29)-NH2. Formation of these metabolites was independent of prior DPP IV hydrolysis but was greatly reduced by trypsin inhibitors. Evaluation of plasma stability of potential GRH super analogs, designed to resist degradation by these enzymes, confirmed that GRH degradation in plasma occurs primarily by DPP IV, and to a lesser extent by trypsin-like enzyme(s).

L9 ANSWER 17 OF 53 MEDLINE on STN

TI Inhibition of mutant p53 expression and growth of DMS-153 small cell lung carcinoma by antagonists of **growth hormone-releasing hormone** and bombesin.

AB We investigated the effects of **growth hormone-releasing hormone** (**GHRH**) antagonists, JV-1-65 and JV-1-63, and bombesin/gastrin-releasing peptide (BN/GRP) antagonist RC-3940-II on DMS-153 **human** small cell lung carcinoma xenografted into nude mice. Treatment with 10 microg/day JV-1-65 or RC-3940-II decreased tumor volume by 28% ($P < 0.05$) and 77% ($P < 0.01$), respectively, after 42 days compared with controls. Combination of JV-1-65 and RC-3940-II induced the greatest inhibition of tumor proliferation (95%; $P < 0.01$), suggesting a synergism. Western blotting showed that the antitumor effects of these antagonists were associated with inhibition of the expression of the mutant tumor suppressor protein p53 (Tp53). Mutation was detected by sequence analysis of the p53 gene at codon 155: ACC [Thr] --> CCC [Pro]. Combination of JV-1-65 and RC-3940-II decreased the levels of mutant p53 protein by 42% ($P < 0.01$) compared with controls. JV-1-65, JV-1-63, and RC-3940-II, given singly, reduced mutant p53 protein expression by 18-24% ($P < 0.05$). Serum insulin-like growth factor (IGF)-I levels were diminished in animals receiving **GHRH** antagonists. mRNA levels for IGF-II, IGF receptor-I, GRP receptor, and EGF receptor in tumors were significantly decreased by combined treatment with JV-1-65 and RC-3940-II. DMS-153 tumors expressed mRNAs for **GHRH** and **GHRH** receptor splice variants 1 and 2, suggesting that **GHRH** could be an autocrine growth factor. Proliferation of DMS-153 cells in vitro was stimulated by GRP and IGF-II and inhibited by JV-1-65. This study indicates that **GHRH** antagonists and BN/GRP antagonist inhibit the growth of DMS-153 small cell lung carcinoma concomitantly with the expression of mutant Tp53, which might uncouple the signal transduction pathways for cell growth stimulation.

L9 ANSWER 18 OF 53 MEDLINE on STN

TI Ectopic secretion of **growth hormone-releasing hormone** (**GHRH**) in neuroendocrine tumors: relevant clinical aspects.

AB The aim of this article is to briefly review the physiology of **growth hormone-releasing hormone** (**GHRH**) and the diagnosis and treatment of **GHRH**-mediated acromegaly. Moreover, the role of **GHRH** and its antagonists in the pathogenesis and treatment of cancer will be reviewed. Hypothalamic **GHRH** is secreted into the portal system, binds to specific surface receptors of the somatotroph cell and elicits intracellular signals that modulate pituitary GH synthesis and/or secretion. **GHRH** -producing neurons have been well characterized in the hypothalamus by immunostaining techniques. Hypothalamic tumors, including hamartomas. choristomas, gliomas. and gangliocitomas. may produce excessive **GHRH** with subsequent GH hypersecretion and resultant acromegaly. **GHRH** is synthesized and expressed in multiple extrapituitary

tissues. Excessive peripheral production of **GHRH** by a tumor source would therefore be expected to cause somatotroph cell hyperstimulation and increased GH secretion. The structure of hypothalamic **GHRH** was infact elucidated from material extracted from pancreatic **GHRH**-secreting tumors in two patients with acromegaly. Immunoreactive **GHRH** is present in several tumors, including carcinoid tumors, pancreatic cell tumors, small-cell lung cancers, adrenal adenomas, and pheochromocitomas which have been reported to secrete **GHRH**. Acromegaly in these patients. however, is uncommon. In a retrospective survey of 177 acromegalic patients only a single patient was identified with elevated plasma **GHRH** levels. Measuring **GHRH** plasma levels therefore provides a precise and cost-effective test for the diagnosis of ectopic acromegaly. Peripheral **GHRH** levels are not elevated in patients with hypothalamic **GHRH**- secreting tumors, supporting the notion that excess eutopic hypothalamic **GHRH** secretion into the hypophyseal portal system does not appreciably enter the systemic circulation. Elevated circulating **GHRH** levels, a normal or small-size pituitary gland, or clinical and biochemical features of other tumors known to be associated with extrapituitary acromegaly, are all indications for extrapituitary imaging. An enlarged pituitary is, however, often found on MRI of patients with peripheral **GHRH**-secreting tumors, and the radiologic diagnosis of a pituitary adenoma may be difficult to exclude. Surgical resection of the tumor secreting ectopic **GHRH** should reverse the hypersecretion of GH, and pituitary surgery should not be necessary in these patients. Nonresectable, disseminated or reccurrent carcinoid syndrome with ectopic **GHRH** secretion can also be managed medically with long-acting somatostatin analogs (octreotide and lanreotide). The presence of **GHRH** and its receptors in several extrahypothalamic tissues, including ovary, testis and the digestive tract, suggests that **GHRH** may have a regulatory role in these tissues. As previously mentioned, biologically or immunologically active **GHRH** and mRNA encoding **GHRH** have been found in several **human** malignant tumors. including cancers of the breast, endometrium and ovary and their cell lines. The synthesis and evaluation of analogs with various modifications revealed that certain hydrophobic and helix-stabilizing **amino acid substitutions** can produce antagonists with increased GH releasing inhibitory potencies and **GHRH** receptor-binding affinities in vitro. The review of experimental results of these substances are promising altrough no clinical data are yet available. Finally, the advent of these antagonists has allowed significant progress in the understanding of the role of the central and tissue **GHRH**-GH-IGFs system in the pathogenesis of tumors.

L9 ANSWER 19 OF 53 MEDLINE on STN

TI Absence of constitutively activating mutations in the **GHRH** receptor in GH-producing pituitary tumors.

AB The molecular events leading to the development of GH-producing pituitary tumors remain largely unknown. We hypothesized that activating mutations of the **GHRH** receptor might occur in a subset of GH-producing pituitary tumors. Genomic DNA samples from 54 GH-producing pituitary tumor tissues were screened for mutations of the **GHRH** receptor. Eleven homozygous or heterozygous nucleotide substitutions [169G > A (A57T), 338C > T (P113L), 363G > T (E121D), 409C > T (H137Y), 547G > A (D183N), 673G > A (V225I), 749G > A (W250X), 760G > A (V254M), 785G > A (S262N), 880G > A (G294R), 1268G > A (C423Y)] were found in 12 patients (22.2%). The 169G > A substitution (A57T) appears to be a polymorphism (4 patients, 7.4%). E121D and V225I were each found in 2 patients. In 1 patient with the V225I sequence, the substitution was not found in genomic DNA from peripheral leukocytes, suggesting a somatic mutation. A patient with a heterozygous W250X mutation was homozygous for the C423Y substitution. These variant **GHRH** receptors were studied in transfected TSA-201 cells to evaluate the functional consequences of the amino acid changes. None of the **GHRH** receptor variants was associated with basal elevation of intracellular cAMP. **GHRH** induced variable cAMP responses. With the W250X and G294R variants, there

was no cAMP stimulation by **GHRH**, indicating that the mutations are inactivating. Expression of the W250X **GHRH** receptor on the cell membrane was severely decreased and **GHRH** binding to the G294R **GHRH** receptor was impaired. Although **GHRH** receptor variants are common in GH- producing pituitary adenomas, constitutively activating mutations, as a mechanism for GH-producing pituitary tumors appear to be rare.

L9 ANSWER 20 OF 53 MEDLINE on STN
TI Molecular cloning of **growth hormone-releasing hormone**/pituitary adenylyl cyclase-activating polypeptide in the frog Xenopus laevis: brain distribution and regulation after castration.
AB Pituitary adenylyl cyclase-activating peptide (PACAP) appears to regulate several neuroendocrine functions in the frog, but its messenger RNA (mRNA) structure and brain distribution are unknown. To understand the potential role of PACAP in the male frog hypothalamic-pituitary-gonadal axis, we cloned the frog Xenopus laevis PACAP mRNA and determined its distribution in the brain. We then analyzed the castration-induced alterations of mRNA expression for PACAP and its selective type I receptor (PAC1) in the hypothalamic anterior preoptic area, a region known to regulate reproductive function. The PACAP mRNA encodes a peptide precursor predicted to give rise to both GH-releasing hormone and PACAP. The deduced peptide sequence of PACAP-38 was nearly identical to that of **human** PACAP with one **amino acid substitution**. Abundant PACAP mRNA was detected in the brain, but not several other tissues, including the testis. In situ hybridization revealed strong expression of the PACAP gene in the dorsal pallium, ventral hypothalamus, and nuclei of cerebellum. PACAP mRNA signals were weak to moderate in the hypothalamic anterior preoptic area and were absent in the pituitary. Castration induced an increase in the expression of PACAP and PAC1 receptor mRNAs in the hypothalamic anterior preoptic area after 3 days. Replacement with testosterone prevented the castration-induced changes. These results provide a molecular basis for studying the physiological functions of PACAP in frog brain and suggest that PACAP may be involved in the feedback regulation of hypothalamic-pituitary-gonadal axis.

=> display l9 21-30 ibib abs
YOU HAVE REQUESTED DATA FROM FILE 'BIOSIS, CAPLUS, MEDLINE, SCISEARCH, EMBASE' - CONTINUE? (Y)/N:y

L9 ANSWER 21 OF 53 MEDLINE on STN
ACCESSION NUMBER: 93351712 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8102338
TITLE: G-proteins and hormonal signalling in **human** pituitary tumors: genetic mutations and functional alterations.
AUTHOR: Spada A; Vallar L; Faglia G
CORPORATE SOURCE: Institute of Endocrine Sciences, Ospedale Maggiore IRCCS, Milan, Italy.
SOURCE: Frontiers in neuroendocrinology, (1993 Jul) 14 (3) 214-32. Ref: 91
Journal code: 7513292. ISSN: 0091-3022.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199309
ENTRY DATE: Entered STN: 19931001
Last Updated on STN: 20000303
Entered Medline: 19930916
AB In the last few years, molecular studies on pituitary adenomas have

yielded several lines of evidence supporting a primary pituitary origin for these tumors. In fact, analyses of x-chromosomal inactivation show that the great majority of pituitary tumors are monoclonal in origin, suggesting that one or more mutations are responsible for the selective expansion of a single cell clone. Mutations constitutively activating GTP-binding proteins have been identified in subsets of pituitary adenomas. Single **amino acid substitutions** replacing Arg 201 with either Cys, His, or Gln 227 with either Arg or Leu of the alpha-subunit of the Gs gene were identified in one third of growth hormone (GH)-secreting adenomas. Both mutations stabilize alpha s in its active conformation by inhibiting GTPase activity, thus mimicking the effect of specific extracellular growth factors, such as **growth hormone releasing hormone (GHRH)**. Since several lines of evidence suggest that cAMP is involved in somatotrope replication, it has been proposed that the alpha s gene can be converted into an oncogene, designated gsp (for Gs protein). Recently, the ras oncogene has been identified in one prolactinoma characterized by unusual invasiveness. Although these data seem to negate a primary role for hypothalamic neurohormones in adenoma formation, it is conceivable that the hormones may exert a role in the sequence of events leading to clonal expansion of a transformed cell. Moreover, alterations in receptor and/or postreceptor events triggered by hypothalamic neurohormones may result in amplification of stimulatory inputs and impairment of inhibitory ones.

L9 ANSWER 22 OF 53 MEDLINE on STN

ACCESSION NUMBER:	93345532 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 8344311
TITLE:	Two salmon neuropeptides encoded by one brain cDNA are structurally related to members of the glucagon superfamily.
AUTHOR:	Parker D B; Coe I R; Dixon G H; Sherwood N M
CORPORATE SOURCE:	Department of Biology, University of Victoria, Canada.
SOURCE:	European journal of biochemistry / FEBS, (1993 Jul 15) 215 (2) 439-48. Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY:	GERMANY: Germany, Federal Republic of
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
OTHER SOURCE:	GENBANK-L09682; GENBANK-L09683; GENBANK-X71336; GENBANK-X71337; GENBANK-X71338; GENBANK-X71339; GENBANK-X71340; GENBANK-X72968; GENBANK-X73157; GENBANK-X73233
ENTRY MONTH:	199309
ENTRY DATE:	Entered STN: 19930924 Last Updated on STN: 19960129 Entered Medline: 19930903

AB A cDNA that codes for two peptides in the glucagon superfamily has been isolated from sockeye salmon brain. The first peptide is related to **growth hormone-releasing hormone** (**GHRH**), which has high sequence similarity with PACAP-related peptide. The second peptide is structurally related to vasoactive intestinal peptide, which is also related to a newly identified peptide in mannals, pituitary adenylate-cyclase-activating polypeptide (PACAP). The salmon precursor contains 173 amino acids and has dibasic and monobasic enzyme-processing sites for cleavage of a 45-amino-acid **GHRH** -like peptide with a free C-terminus and a 38-amino-acid PACAP with an amidated C-terminus. The salmon **GHRH**-like peptide has 40% amino acid sequence identity with a **human GHRH** and 56% identity with **human** PACAP-related peptide. The 38-amino-acid salmon PACAP is highly conserved (89-92% identity) with only three or four **amino acid substitutions** compared with the **human, ovine** and rat 38-amino-acid PACAP. Not previously reported for mammalian species, a short precursor coding for only one peptide exists in salmon in addition to the long precursor coding for two peptides. In the short precursor, the coding region for

GHRH is deleted leaving the PACAP-coding region in a correct reading frame. This provides one possible control mechanism for an increased expression of one peptide (PACAP) without the concomitant increase in the other peptide (**GHRH**) as occurs in a double-peptide precursor. The importance of the 3' non-translated region of the salmon **GHRH**/PACAP precursor in the regulation of translation is suggested by its 70% nucleotide sequence identity to the 3' non-translated regions of the mammalian PACAP precursors. The structural organization of the salmon **GHRH**/PACAP precursor provides a possible evolutionary scheme for precursors that contain tandem peptides in the glucagon superfamily.

L9 ANSWER 23 OF 53 MEDLINE on STN
ACCESSION NUMBER: 93043898 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1421808
TITLE: Potent agonists of **growth hormone-releasing hormone**. II.
AUTHOR: Zarandi M; Serfozo P; Zsigo J; Deutch A H; Janaky T; Olsen D B; Bajusz S; Schally A V
CORPORATE SOURCE: Veterans Affairs Medical Center, New Orleans, LA 70146.
CONTRACT NUMBER: DK 07467 (NIDDK)
SOURCE: Peptide research, (1992 Jul-Aug) 5 (4) 190-3.
Journal code: 8913494. ISSN: 1040-5704.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921223

AB Analogs of the 29-amino acid sequence of **growth hormone-releasing hormone** (GH-RH) with agmatine (Agm) or Lys-NH2 in position 29 have been synthesized by the solid-phase method, purified, and tested in vitro. Except for one peptide, all analogs contained desaminotyrosine (Dat) in position 1. All contained Nle27 in order to avoid oxidation of Met27. Some peptides contained one or more additional L- or D-**amino acid substitutions** in positions 2, 12, 15, 21, 27 and/or 28. Analogs [Dat1, Ala15, Nle27, Asn28]GH-RH(1-28)Agm (II, [Asn28]-Mz-2-51); [Dat1, Ala15, D-Lys21, Nle27, Asn28]GH-RH(1-28)Agm (III, MZ-3-125); and [Dat1, D-Asn8, Ala15, D-Lys21, Nl27, Asn28]GH-RH(1-28)Agm(IV, MZ-3-129) were 5.7, 2.8, and 3.9 times more potent in vitro, respectively, than GH-RH(1-29)NH2. However, if we compare the potencies of peptides II and III (analogs of the **bovine** sequence) with those of the analogs of **human** GH-RH (XII and XIII) [Dat1, Ala15, Nle27]GH-RH(1-28)Agm; [Dat1, Ala15, D-Lys21, Nle27]GH-RH(1-28)Agm, respectively, the GH-releasing potency was decreased by 50% and 33%, respectively, by the incorporation of Asn28. Our studies indicate that Lys-NH2 at the C-terminus of GH-RH(1-29) and/or beta-Ala, GABA (gamma-aminobutyric acid), and Phe in position 15 are disadvantageous, but potent GH-RH analogs can result from the combination of agmatine in position 29 with other substitutions.

L9 ANSWER 24 OF 53 MEDLINE on STN
ACCESSION NUMBER: 89214680 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2565342
TITLE: Dipeptidylpeptidase IV and trypsin-like enzymatic degradation of **human growth hormone-releasing hormone** in plasma.
AUTHOR: Frohman L A; Downs T R; Heimer E P; Felix A M
CORPORATE SOURCE: Department of Internal Medicine, University of Cincinnati College of Medicine, Ohio 45267.
CONTRACT NUMBER: AM-30067 (NIADDK)
SOURCE: Journal of clinical investigation, (1989 May) 83 (5) 1533-40.
Journal code: 7802877. ISSN: 0021-9738.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198906
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 20000303
Entered Medline: 19890605

AB The plasma enzyme responsible for primary proteolytic cleavage of **growth hormone-releasing hormone** (GRH) at the 2-3 amino acid bond was characterized. Native GRH[GRH(1-44)-NH2 and GRH(1-40)-OH], and COOH-terminally shortened fragments [GRH(1-32)-NH2 and GRH(1-29)-NH2] were rapidly cleaved, while GRH(2-32)-NH2 was not degraded at this site. Moreover, degradation to GRH(3-44)-NH2 was unaffected by an aminopeptidase inhibitor, indicating that this metabolite was generated from a single step cleavage by a dipeptidylpeptidase (DPP) rather than sequential aminopeptidase cleavages. Conversion to GRH(3-44)-NH2 was blocked by diprotin A, a DPP type IV (DPP IV) competitive inhibitor. D-**Amino acid substitution** at either position 1 or 2 also prevented hydrolysis, characteristic of DPP IV. Analysis of endogenous plasma GRH immunoreactivity from a **human** GRH transgenic pig revealed that the major peak coeluted with GRH(3-44)-NH2. Native GRH exhibited trypsin-like degradation at the 11-12 position but cleavage at the 12-13 site occurred only with GRH(1-32)-NH2 and GRH(1-29)-NH2. Formation of these metabolites was independent of prior DPP IV hydrolysis but was greatly reduced by trypsin inhibitors. Evaluation of plasma stability of potential GRH super analogues, designed to resist degradation by these enzymes, confirmed that GRH degradation in plasma occurs primarily by DPP IV, and to a lesser extent by trypsin-like enzyme(s).

L9 ANSWER 25 OF 53 MEDLINE on STN
ACCESSION NUMBER: 87052488 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3096623
TITLE: The effect of intravenous, subcutaneous, and intranasal GH-RH analog, [Nle27]**GHRH**(1-29)-NH2, on growth hormone secretion in normal men: dose-response relationships.
AUTHOR: Vance M L; Evans W S; Kaiser D L; Burke R L; Rivier J; Vale W; Thorner M O
CONTRACT NUMBER: AM 26741 (NIADDK)
HD17120-02 (NICHD)
RO1 AM 32632 (NIADDK)
+
SOURCE: Clinical pharmacology and therapeutics, (1986 Dec) 40 (6) 627-33.
Journal code: 0372741. ISSN: 0009-9236.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198701
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19970203
Entered Medline: 19870114

AB A 29 amino acid analog of **growth hormone releasing hormone** (GH-RH)-40 was given intravenously, subcutaneously, and intranasally to normal men to determine its effectiveness in stimulating growth hormone (GH) release. The GH-RH analog, [Nle27]GH-RH(1-29)-NH2, is an amidated 29 amino acid peptide that has one **amino acid substitution** at position 27. This peptide stimulates GH secretion when given by the intravenous, subcutaneous, and intranasal routes without adverse effect. The degree of GH stimulation was variable among subjects and the greatest amount of stimulation occurred with the highest doses. GH stimulation occurred in a dose-responsive manner after all three routes of administration. A tenfold higher subcutaneous dose was required to stimulate a comparable

amount of GH secretion as compared with intravenous administration, and a thirtyfold higher intranasal than intravenous dose was required to stimulate approximately one fifth the amount of GH release. For comparison, one dose of GH-RH-40, 1 microgram/kg, was administered intravenously. GH secretion after 1 microgram/kg GH-RH-40 and 1 microgram/kg Nle27 GH-RH was comparable between the two groups of subjects. Stimulation of GH secretion by Nle27 GH-RH occurred within 5 minutes of intravenous and within 10 minutes of subcutaneous and intranasal administration; peak GH levels were observed within 30 minutes. GH levels declined and returned to near baseline levels 2 hours after administration of the analog.(ABSTRACT TRUNCATED AT 250 WORDS)

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ACCESSION NUMBER: 2001:954668 SCISEARCH
THE GENUINE ARTICLE: 497ZT
TITLE: Ectopic secretion of **growth hormone-releasing hormone** (**GHRH**) in neuroendocrine tumors: Relevant clinical aspects
AUTHOR: Doga M; Bonadonna S; Burattin A; Giustina A (Reprint)
CORPORATE SOURCE: Spedali Civil Brescia, Endocrine Sect Med 2A, I-25125 Brescia, Italy (Reprint); Univ Brescia, Dept Internal Med, Endocrine Sect, I-25121 Brescia, Italy
COUNTRY OF AUTHOR: Italy
SOURCE: ANNALS OF ONCOLOGY, (2001) Vol. 12, Supp. [2], pp. S89-S94

ISSN: 0923-7534.
PUBLISHER: KLUWER ACADEMIC PUBL, VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 53
ENTRY DATE: Entered STN: 14 Dec 2001
Last Updated on STN: 14 Dec 2001

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The aim of this article is to briefly review the physiology of **growth hormone-releasing, hormone** (**GHRH**) and the diagnosis and treatment of **GHRH**-mediated acromegaly. Moreover, the role of **GHRH** and its antagonists in the pathogenesis and treatment of cancer will be reviewed. Hypothalamic **GHRH** is secreted into the portal system, binds to specific surface receptors of the somatotroph cell and elicits intracellular signals that modulate pituitary GH synthesis and/or secretion. **GHRH** -producing neurons have been well characterized in the hypothalamus by immunostaining techniques. Hypothalamic tumors, including hamartomas, choristomas, gliomas, and gangliocitomas, may produce excessive **GHRH** with subsequent GH hypersecretion and resultant acromegaly. **GHRH** is synthesized and expressed in multiple extrapituitary tissues.

Excessive peripheral production of **GHRH** by a tumor source would therefore be expected to cause somatotroph cell hyperstimulation and increased GH secretion. The structure of hypothalamic **GHRH** was infact elucidated from material extracted from pancreatic **GHRH** -secreting tumors in two patients with acromegaly, Immunoreactive **GHRH** is present in several tumors, including carcinoid tumors, pancreatic cell tumors, small-cell lung cancers, adrenal adenomas, and pheochromocitomas which have been reported to secrete **GHRH**. Acromegaly in these patients, however, is uncommon. In a retrospective survey of 177 acromegalic patients only a single patient was identified with elevated plasma **GHRH** levels. Measuring **GHRH** plasma levels therefore provides a precise and cost-effective test for the diagnosis of ectopic acromegaly. Peripheral **GHRH** levels are not elevated in patients with hypothalamic **GHRH**-secreting tumors, supporting the notion that excess eutopic hypothalamic **GHRH** secretion into the hypophyseal portal system does not appreciably enter the systemic circulation. Elevated circulating **GHRH** levels, a normal or small-size pituitary gland, or clinical and biochemical features

of other tumors known to be associated with extrapituitary acromegaly, are all indications for extrapituitary imaging. An enlarged pituitary is, however, often found on MRI of patients with peripheral **GHRH** -secreting tumors, and the radiologic diagnosis of a pituitary adenoma may be difficult to exclude. Surgical resection of the tumor secreting ectopic **GHRH** should reverse the hypersecretion of GH, and pituitary surgery should not be necessary in these patients. Nonresectable, disseminated or reccurrent carcinoid syndrome with ectopic **GHRH** secretion can also be managed medically with long-acting somatostatin analogs (octreotide and lanreotide). The presence of **GHRH** and its receptors in several extrahypothalamic tissues, including ovary, testis and the digestive tract, suggests that **GHRH** may have a regulatory role in these tissues. As previously mentioned, biologically or immunologically active **GHRH** and mRNA encoding **GHRH** have been found in several **human** malignant tumors, including cancers of the breast, endometrium and ovary and their cell lines. The synthesis and evaluation of analogs with various modifications revealed that certain hydrophobic and helix-stabilizing **amino acid substitutions** can produce antagonists with increased GH releasing inhibitory potencies and **GHRH** receptor-binding affinities in vitro. The review of experimental results of these substances are promising altrough no clinical data are yet available. Finally, the advent of these antagonists has allowed significant progress in the understanding of the role of the central and tissue **GHRH**-GH-IGFs system in the pathogenesis of tumors.

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ACCESSION NUMBER: 2000:648467 SCISEARCH
THE GENUINE ARTICLE: 346LE
TITLE: Molecular cloning of **growth hormone-releasing hormone**/pituitary adenylyl cyclase-activating polypeptide in the frog Xenopus laevis: Brain distribution and regulation after castration
AUTHOR: Hu Z T; Lelievre V; Tam J; Cheng J W; Fuenzalida G; Zhou X R; Waschek J A (Reprint)
CORPORATE SOURCE: Univ Calif Los Angeles, Dept Psychiat, Sch Med, Mental Retardat Res Ctr, 68-225 NPI, 760 Westwood Plaza, Los Angeles, CA 90024 USA (Reprint); Univ Calif Los Angeles, Dept Psychiat, Sch Med, Mental Retardat Res Ctr, Los Angeles, CA 90024 USA
COUNTRY OF AUTHOR: USA
SOURCE: ENDOCRINOLOGY, (SEP 2000) Vol. 141, No. 9, pp. 3366-3376. ISSN: 0013-7227.
PUBLISHER: ENDOCRINE SOC, 4350 EAST WEST HIGHWAY SUITE 500, BETHESDA, MD 20814-4110 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 57
ENTRY DATE: Entered STN: 2000
Last Updated on STN: 2000

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Pituitary adenylyl cyclase-activating peptide (PACAP) appears to regulate several neuroendocrine functions in the frog, but its messenger RNA (mRNA) structure and brain distribution are unknown. To understand the potential role of PACAP in the male frog hypothalamic-pituitary-gonadal axis, we cloned the frog Xenopus laevis PACAP mRNA and determined its distribution in the brain. We then analyzed the castration-induced alterations of mRNA expression for PACAP and its selective type I receptor (PAC(1)) in the hypothalamic anterior preoptic area, a region known to regulate reproductive function. The PACAP mRNA encodes a peptide precursor predicted to give rise to both GH-releasing hormone and PACAP. The deduced peptide sequence of PACAP-38 was nearly identical to that of **human** PACAP with one **amino acid substitution**. Abundant PACAP mRNA was detected in the brain, but not several other tissues, including the testis. In situ hybridization

revealed strong expression of the PACAP gene in the dorsal pallium, ventral hypothalamus, and nuclei of cerebellum PACAP mRNA signals were weak to moderate in the hypothalamic anterior preoptic area and were absent in the pituitary. Castration induced an increase in the expression of PACAP and PAC(1) receptor mRNAs in the hypothalamic anterior preoptic area after 3 days. Replacement with testosterone prevented the castration induced changes. These results provide a molecular basis for studying the physiological functions of PACAP in frog brain and suggest that PACAP may be involved in the feedback regulation of hypothalamic-pituitary-gonadal axis.

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ACCESSION NUMBER: 1993:476146 SCISEARCH
THE GENUINE ARTICLE: LP342
TITLE: 2 SALMON NEUROPEPTIDES ENCODED BY ONE BRAIN CDNA ARE STRUCTURALLY RELATED TO MEMBERS OF THE GLUCAGON SUPERFAMILY
AUTHOR: PARKER D B (Reprint); COE I R; DIXON G H; SHERWOOD N M
CORPORATE SOURCE: UNIV VICTORIA, DEPT BIOL, POB 1700, VICTORIA V8W 2Y2, BC, CANADA (Reprint); UNIV CALGARY, HLTH SCI CTR, DEPT MED BIOCHEM, CALGARY T2N 1N4, ALBERTA, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (15 JUL 1993) Vol. 215, No. 2, pp. 439-448.
ISSN: 0014-2956.
PUBLISHER: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 61
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A cDNA that codes for two peptides in the glucagon superfamily has been isolated from sockeye salmon brain. The first peptide is related to **growth hormone-releasing hormone** (**GHRH**), which has high sequence similarity with PACAP-related peptide. The second peptide is structurally related to vasoactive intestinal peptide, which is also related to a newly identified peptide in mannals, pituitary adenylate-cyclase-activating polypeptide (PACAP). The salmon precursor contains 173 amino acids and has dibasic and monobasic enzyme-processing sites for cleavage of a 45-amino-acid **GHRH** -like peptide with a free C-terminus and a 38-amino-acid PACAP with an amidated C-terminus. The salmon **GHRH**-like peptide has 40% amino acid sequence identity with the **human GHRH** and 56% identity with **human** PACAP-related peptide. The 38-amino-acid salmon PACAP is highly conserved (89-92% identity) with only three or four **amino acid substitutions** compared with the **human, ovine** and rat 38-amino-acid PACAP.

Not previously reported for mammalian species, a short precursor coding for only one peptide exists in salmon in addition to the long precursor coding for two peptides. In the short precursor, the coding region for **GHRH** is deleted leaving the PACAP-coding region in a correct reading-frame. This provides one possible control mechanism for an increased expression of one peptide (PACAP) without the concomitant increase in the other peptide (**GHRH**) as occurs in a double-peptide precursor. The importance of the 3' non-translated region of the salmon **GHRH**/PACAP precursor in the regulation of translation is suggested by its 70% nucleotide sequence identity to the 3' non-translated regions of the mammalian PACAP precursors. The structural organization of the salmon **GHRH**/PACAP precursor provides a possible evolutionary scheme for precursors that contain tandem peptides in the glucagon superfamily.

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ACCESSION NUMBER: 1993:415287 SCISEARCH
THE GENUINE ARTICLE: LJ982
TITLE: G-PROTEINS AND HORMONAL SIGNALING IN **HUMAN** PITUITARY-TUMORS - GENETIC MUTATIONS AND FUNCTIONAL ALTERATIONS
AUTHOR: SPADA A (Reprint); VALLAR L; FAGLIA G
CORPORATE SOURCE: OSPED MAGGIORE, IRCCS, INST ENDOCRINE SCI, VIA F SFORZA 35, I-20122 MILAN, ITALY (Reprint); UNIV MILAN, SCI INST SAN RAFFAELE, CNR, CTR CYTOPHARMACOL, DEPT PHARMACOL, I-20122 MILAN, ITALY
COUNTRY OF AUTHOR: ITALY
SOURCE: FRONTIERS IN NEUROENDOCRINOLOGY, (JUL 1993) Vol. 14, No. 3, pp. 214-232.
ISSN: 0091-3022.
PUBLISHER: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 90
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In the last few years, molecular studies on pituitary adenomas have yielded several lines of evidence supporting a primary pituitary origin for these tumors. In fact, analyses of x-chromosomal inactivation show that the great majority of pituitary tumors are monoclonal in origin, suggesting that one or more mutations are responsible for the selective expansion of a single cell clone. Mutations constitutively activating GTP-binding proteins have been identified in subsets of pituitary adenomas. Single **amino acid substitutions** replacing Arg 201 with either Cys, His, or Gln 227 with either Arg or Leu of the alpha-subunit of the Gs gene were identified in one third of growth hormone (GH)-secreting adenomas. Both mutations stabilize alphas in its active conformation by inhibiting GTPase activity, thus mimicking the effect of specific extracellular growth factors, such as **growth hormone releasing hormone (GHRH)**. Since several lines of evidence suggest that cAMP is involved in somatotrope replication, it has been proposed that the alphas gene can be converted into an oncogene, designated gsp (for Gs protein). Recently, the ras oncogene has been identified in one prolactinoma characterized by unusual invasiveness. Although these data seem to negate a primary role for hypothalamic neurohormones in adenoma formation, it is conceivable that the hormones may exert a role in the sequence of events leading to clonal expansion of a transformed cell. Moreover, alterations in receptor and/or postreceptor events triggered by hypothalamic neurohormones may result in amplification of stimulatory inputs and impairment of inhibitory ones.

L9 ANSWER 30 OF 53 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1992:477749 SCISEARCH
THE GENUINE ARTICLE: JH085
TITLE: POTENT AGONISTS OF **GROWTH HORMONE-RELEASING HORMONE** .2.
AUTHOR: ZARANDI M; SERFOZO P; ZSIGO J; DEUTCH A H; JANAKY T; OLSEN D B; BAJUSZ S; SCHALLY A V (Reprint)
CORPORATE SOURCE: VET AFFAIRS MED CTR, 1601 PERDIDO ST, NEW ORLEANS, LA 70146 (Reprint); TULANE UNIV, NEW ORLEANS, LA 70118; WR GRACE & CO, CONN WASHINGTON RES CTR, COLUMBIA, MD
COUNTRY OF AUTHOR: USA
SOURCE: PEPTIDE RESEARCH, (JUL-AUG 1992) Vol. 5, No. 4, pp. 190-193.
ISSN: 1040-5704.
PUBLISHER: EATON PUBLISHING CO, 154 E. CENTRAL ST, NATICK, MA 01760.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE

LANGUAGE: English
REFERENCE COUNT: 19
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Analogs of the 29-amino acid sequence of **growth hormone-releasing hormone** (GH-RH) with agmatine (Agm) or Lys-NH2 in position 29 have been synthesized by the solid-phase method, purified, and tested in vitro. Except for one peptide, all analogs contained desaminotyrosine (Dat) in position 1. All contained Nle27 in order to avoid oxidation of Met27 Some peptides contained one or more additional L- or D-**amino acid substitutions** in positions 2, 12, 15, 21, 27 and/or 28. Analogs [Dat1, Ala15, Nle27, Asn28]GH-RH(1-28)Agm (II, [Asn28]-Mz-2-51); [Dat1, Ala15, D-Lys21, Nle27, Asn28]GH-RH(1-28)Agm (III, MZ-3-125); and [Dat1, D-Asn8, Ala15, D-Lys21, Nle27, Asn28]GH-RH(1-28)Agm (IV, MZ-3-129) were 5.7, 2.8, and 3.9 times more potent in vitro, respectively, than GH-RH(1-29)NH2. However, if we compare the potencies of peptides II and III (analogs of the **bovine** sequence) with those of the analogs of **human** GH-RH (XII and XIII) [Dat1, Ala15, Nle27]**GHRH** (1-28)Agm; [Dat1, Ala15, D-Lys21, Nle27]GH-RH(1-28)Agm, respectively, the GH-releasing potency was decreased by 50% and 33%, respectively, by the incorporation of Asn28. Our studies indicate that Lys-NH2 at the C-terminus of GH-RH(1-29) and/or beta-Ala, GABA (gamma-aminobutyric acid), and Phe in position 15 are disadvantageous, but potent GH-RH analogs can result from the combination of agmatine in position 29 with other substitutions.

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L9 ANSWER 31 OF 53 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1991:20779 SCISEARCH
THE GENUINE ARTICLE: EQ055
TITLE: SYNTHESIS AND INVITRO AND INVIVO ACTIVITY OF ANALOGS OF **GROWTH HORMONE-RELEASING HORMONE** (GH-RH) WITH C-TERMINAL AGMATINE
AUTHOR: ZARANDI M (Reprint); CSERNUS V; BOKSER L; BAJUSZ S; GROOT K; SCHALLY A V
CORPORATE SOURCE: VET ADM MED CTR, INST ENDOCRINE POLYPEPTIDE & CANC, 1601 PERDIDO ST, NEW ORLEANS, LA 70146; TULANE UNIV, SCH MED, DEPT MED, EXPTL MED SECT, NEW ORLEANS, LA 70112
COUNTRY OF AUTHOR: USA
SOURCE: INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, (DEC 1990) Vol. 36, No. 6, pp. 499-505.
ISSN: 0367-8377.
PUBLISHER: MUNKSGAARD INT PUBL LTD, 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 23
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In the search for more active analogs of **human growth hormone-releasing hormone** (GH-RH), 37 new compounds were synthesized by solid phase methodology, purified, and tested biologically. Most of the analogs contained a sequence of 27 amino acids and N-terminal desaminotyrosine (Dat) and C-terminal agmatine (Agm), which are not amino acids. In addition to Dat in position 1 and Agm in position 29, the majority of the analogs had

Ala15 and Nle27 substitutions and one or more additional L- or D-amino acid modifications. [Dat1, Ala15, Nle27]GH-RH(1-28)Agm (MZ-2-51) was the most active analog. Its in vitro GH-releasing potency was 10.5 times higher than that of GH-RH(1-29)NH2 and in the i.v. in vivo assay, MZ-2-51 was 4-5 times more active than the standard. After s.c. administration to rats, MZ-2-51 showed an activity 34 times higher at 15 min and 179 times greater at 30 min than GH-RH(1-29)NH2 and also displayed a prolonged activity. D-Tyr10, D-Lys12, and D-Lys21 homologs of MZ-2-51 also showed enhanced activities. Thus, [Dat1, D-Tyr10, Ala15, Nle27]GH-RH(1-28)Agm (MZ-2-159), [Dat1, D-Lys12, Ala15, Nle27]GH-RH(1-28)AGM (MZ-2-57), and [Dat1, Ala15, D-Lys21, Nle27]GH-RH(1-28)Agm (MZ-2-75) were 4-6 times more active in vitro than GH-RH(1-29)NH2. In vivo, after i.v. administration, analog MZ-2-75 was equipotent and analogs MZ-2-159 and MZ-2-57 about twice as potent as the standard. After s.c. administration, the potencies of MZ-2-57 and MZ-2-75 were 10-14 times higher than the standard at 15 min and 45-89 times greater when determined at 30 min. Most of the analogs containing two or more D-**amino acid substitutions** were less active than GH-RH(1-29)NH2 or inactive. Our studies indicate that very potent GH-RH analogs can result from the combination of agmatine in position 29 with other substitutions.

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ACCESSION NUMBER: 2005222634 EMBASE
TITLE: Homozygous and heterozygous expression of a novel insulin-like growth factor-I mutation.
AUTHOR: Walenkamp M.J.E.; Karperien M.; Pereira A.M.; Hilhorst-Hofstee Y.; Van Doorn J.; Chen J.W.; Mohan S.; Denley A.; Forbes B.; Van Duyvenvoorde H.A.; Van Thiel S.W.; Sluimers C.A.; Bax J.J.; De Laat J.A.P.M.; Breuning M.B.; Romijn J.A.; Wit J.M.
CORPORATE SOURCE: M.J.E. Walenkamp, Department of Pediatrics J6-S, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, Netherlands. m.j.e.walenkamp@lumc.nl
SOURCE: Journal of Clinical Endocrinology and Metabolism, (2005) Vol. 90, No. 5, pp. 2855-2864.
Refs: 60
ISSN: 0021-972X CODEN: JCEMAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050609
Last Updated on STN: 20050609

AB IGF-I is a key factor in intrauterine development and post-natal growth and metabolism. The secretion of IGF-I in utero is not dependent on GH, whereas in childhood and adult life, IGF-I secretion seems to be mainly controlled by GH, as revealed from studies on patients with **GHRH** receptor and GH receptor mutations. In a 55-yr-old male, the first child of consanguineous parents, presenting with severe intrauterine and postnatal growth retardation, microcephaly, and sensorineural deafness, we found a homozygous G to A nucleotide substitution in the IGF-I gene changing valine 44 into methione. The inactivating nature of the mutation was proven by functional analysis demonstrating a 90-fold reduced affinity of recombinantly produced for the IGF-I receptor. Additional investigations revealed osteoporosis, a partial gonadal dysfunction, and a relatively well-preserved cardiac function. Nine of the 24 relatives studied carried the mutation. They had a significantly lower birth weight, final height, and head circumference than noncarriers. In conclusion, the phenotype of our patient consists of severe intrauterine growth retardation, deafness, and mental retardation, reflecting the GH-independent secretion of IGF-I in utero. The postnatal growth pattern, similar to growth of untreated GH-deficient or GH-insensitive children, is in agreement with the hypothesis that IGF-I secretion in childhood is mainly GH dependent. Remarkably, IGF-I deficiency is relatively well

tolerated during the subsequent four decades of adulthood. IGF-I haploinsufficiency results in subtle inhibition of intrauterine and postnatal growth. Copyright .COPYRGT. 2005 by The Endocrine Society.

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ACCESSION NUMBER: 2004087314 EMBASE
TITLE: Increased activity of antagonists of **growth hormone-releasing hormone** substituted at positions 8, 9, and 10.
AUTHOR: Varga J.L.; Schally A.V.; Horvath J.E.; Kovacs M.; Halmos G.; Groot K.; Toller G.L.; Rekasi Z.; Zarandi M.
CORPORATE SOURCE: A.V. Schally, Endocr., Polypeptide, Cancer Inst., Veterans Affairs Medical Center, Tulane University School of Medicine, New Orleans, LA 70112-2699, United States
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (10 Feb 2004) Vol. 101, No. 6, pp. 1708-1713.
Refs: 26
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040318
Last Updated on STN: 20040318

AB Antagonists of **human growth hormone-releasing hormone** (hGHRH) with increased potency and improved enzymatic and chemical stability are needed for potential clinical applications. We synthesized 21 antagonistic analogs of hGHRH(1-29)NH2, substituted at positions 8, 9, and 10 of the common core sequence {phenylacetyl-Tyr(1), D-Arg(2,28), para-chloro-phenylalanine 6, Arg(9)/homoarginine 9, Tyr (10)/O-methyl-tyrosine 10, α-aminobutyric acid 15, norleucine 27, Har(29)} hGHRH(1-29)NH(2). Inhibitory effects on hGHRH-induced GH release were evaluated in vitro in a su perfused rat pituitary system, as well as in vivo after i.v. injection into rats. The binding affinities of the peptides to pituitary **GHRH** receptors were also determined. Introduction of para-amidinophenylalanine 10 yielded antagonists JV-1-62 and -63 with the highest activities in vitro and lowest receptor dissociation constants (K(i) = 0.057-0.062 nM). Antagonists JV-1-62 and -63 also exhibited the strongest effect in vivo, significantly ($P < 0.05$-0.001) inhibiting hGHRH-induced GH release for at least 1 h. Para-amino-phenylalanine 10 and O-ethyltyrosine 10 substitutions yielded antagonists potent in vitro, but His(10), 3,3'-diphenylalanine 10, 2-naphthylalanine 10, and cyclohexylalanine 10 modifications were detrimental. Antagonists containing citrulline 9 (in MZ-J-7-72), amidinophenylalanine 9 (in JV-1-65), His (9), D-Arg(9), citrulline 8, Ala(8), D-Ala (8), or α-aminobutyric acid 8 substituents also had high activity and receptor affinity in vitro. However, in vitro potencies of analogs with substitution in position 9 correlated poorly with acute endocrine effects in vivo, as exemplified by the weak and/or short inhibitory actions of antagonists JV-1-65 and MZ-J-7-72 on GH release in vivo. Nevertheless, antagonist JV-1-65 was more potent than JV-1-63 in tests on inhibition of the growth of **human** prostatic and lung cancer lines xenografted into nude mice. This indicates that oncological activity may be based on several mechanisms. hGHRH antagonists with improved efficacy could be useful for treatment of cancers that depend on insulin-like growth factors or **GHRH**.

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ACCESSION NUMBER: 2003067799 EMBASE
TITLE: A new missense mutation in the **growth hormone-releasing hormone**

receptor gene in familial isolated GH deficiency.
AUTHOR: Carakushansky M.; Whatmore A.J.; Clayton P.E.; Shalet S.M.; Gleeson H.K.; Price D.A.; Levine M.A.; Salvatori R.
CORPORATE SOURCE: R. Salvatori, Division of Endocrinology, Johns Hopkins Univ. Sch. of Medicine, 1830 East Monument Street 333, Baltimore, MD 21287, United Kingdom. salvator@jhmi.edu
SOURCE: European Journal of Endocrinology, (1 Jan 2003) Vol. 148, No. 1, pp. 25-30.
Refs: 22
ISSN: 0804-4643 CODEN: EJOEEP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030220
Last Updated on STN: 20030220

AB Objective: Mutations in the GH-releasing hormone (**GHRH**) receptor (GHRHR) gene (GHRHR) cause autosomal recessive familial isolated GH deficiency (IGHD). We searched for GHRHR mutations in two siblings with IGHD type IB and a history of parental consanguinity. Design: We analyzed peripheral genomic DNA of an index patient. After identifying a novel mutation in the GHRHR, we performed functional studies in order to confirm that the mutation causes receptor malfunction. Methods: The entire GHRHR was analyzed in the index case by denaturing gradient gel electrophoresis. Abnormally migrating bands were isolated and sequenced. The mutated area was then sequenced in all family members whose DNA was available. The newly found mutation was inserted into a GHRHR cDNA. Wild-type and mutant cDNAs were expressed into CHO cells and the cyclic AMP (cAMP) response to **GHRH** was measured. In order to determine whether the mutant receptor was properly expressed on the cell membrane surface, CHO cells were transfected with wild-type or mutant Results: Both patients were homozygous for a new missense mutation in codon 176, corresponding to the second transmembrane domain of the receptor protein that replaces alanine with valine (A176V). The mother and three unaffected siblings were heterozygous for the mutation; DNA from the father was not available. Cells expressing the A176V receptor had a significantly reduced cAMP response to **GHRH**, despite appropriate expression on the cell surface. Conclusions: We describe two siblings with IGHD due to a new mutation in the GHRHR that disrupts **GHRH** signaling and leads to **GHRH** resistance.

L9 ANSWER 35 OF 53 EMBASE
on STN
ACCESSION NUMBER: 2002386365 EMBASE
TITLE: A polymorphism in the **growth hormone-releasing hormone** receptor gene: Clinical significance?.
AUTHOR: Adams E.F.; Oikonomou E.; Bhamrah M.; Buchfelder M.; Mitchell R.; Poyner D.R.
CORPORATE SOURCE: E.F. Adams, Pharmaceutical Sci. Research Inst., Aston University, Aston Triangle, Birmingham B4 7ET, United Kingdom. e.f.adams@aston.ac.uk
SOURCE: Regulatory Peptides, (15 Oct 2002) Vol. 108, No. 2-3, pp. 125-128.
Refs: 14
ISSN: 0167-0115 CODEN: REPPDY
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005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20021114
Last Updated on STN: 20021114

AB Two forms of the **growth hormone-releasing hormone** (**GHRH**) receptor (**GHRH**-R) exist in terms of a polymorphism at codon 57. The most common allele possesses GCG, coding for Ala. This codon can also be ACG, replacing the Ala with Thr. The present study demonstrates that the latter occurs in about 20% of pituitary somatotrophinomas, removed from patients with acromegaly. Somatotrophinomas possessing the alternative allele respond, on average, more strongly to **GHRH** in terms of GH secretion in vitro than tumors which are homozygous for the more common allele. The distribution of the two allelic forms of the **GHRH**-R did not significantly differ between acromegalic and non-acromegalic subjects. Thus, while the alternative allelic forms may, at least partially, contribute to the variable response of serum GH levels to i.v. **GHRH** observed in acromegalic and normal subjects, it is unlikely that subjects possessing the rarer form containing Thr in place of Ala at residue 57 are at increased risk of developing acromegaly.

L9 ANSWER 36 OF 53 EMBASE
on STN

ACCESSION NUMBER: 2002187766 EMBASE
TITLE: SOM230: A novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile.
AUTHOR: Bruns C.; Lewis I.; Briner U.; Meno-Tetang G.; Weckbecker G.
CORPORATE SOURCE: C. Bruns, Novartis Pharma AG, Research Transplantation, WSJ-386, CH-4002 Basel, Switzerland. Christian.Bruns@pharma.novartis.com
SOURCE: European Journal of Endocrinology, (2002) Vol. 146, No. 5, pp. 707-716.
Refs: 43
ISSN: 0804-4643 CODEN: EJOEEP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020606
Last Updated on STN: 20020606

AB Objective: The aim of the present study was to identify a small, metabolically stable somatotropin release inhibiting factor (SRIF) analog with a more universal binding profile similar to that of natural somatostatin, resulting in improved pharmacological properties and hence new therapeutic uses. Design: A rational drug design approach was followed by synthesizing alanine-substituted SRIF-14 analogs to determine the importance of single amino acids in SRIF-14 for SRIF receptor subtype binding. The incorporation of structural elements of SRIF-14 in a stable cyclohexapeptide template in the form of modified unnatural amino acids resulted in the identification of the novel cyclohexapeptide SOM230. Results: SOM230 binds with high affinity to SRIF receptor subtypes sst1, sst2, sst3 and sst5 and displays a 30- to 40-fold higher affinity for sst1 and sst5 than Sandostatin (octreotide; SMS 201-995) or Somatuline (BIM 23014). In vitro, SOM230 effectively inhibited the **growth hormone releasing hormone** (**GHRH**)-induced growth hormone (GH) release in primary cultures of rat pituitary cells with an IC(50) of 0.4 ± 0.1 nmol/l (n = 5). In vivo, SOM230 also potently suppressed GH secretion in rats. The ED(50) values determined at 1 h and 6 h post injection of SOM230 indicated its very long duration of action in vivo. This property was also reflected in pharmacokinetic studies comparing plasma levels of SMS 201-995 and SOM230 after subcutaneous application. Whereas SMS 201-995 had a terminal elimination half life of 2 h, this was markedly prolonged in SOM230-treated animals

(t(1/2) = 23 h). Furthermore, in rats SOM230 demonstrated a much higher efficacy in lowering plasma insulin-like growth factor-I (IGF-I) levels compared with SMS 201-995. The infusion of 10 μg/kg/h of SOM230 using subcutaneously implanted minipumps decreased plasma IGF-I levels far more effectively than SMS 201-995. After 126 days of continuous infusion of SOM230 plasma IGF-I levels were decreased by 75% of placebo-treated control animals. For comparison SMS 201-995, when used under the same experimental conditions, resulted in only a 28% reduction of plasma IGF-I levels, indicating a much higher efficacy for SOM230 in this animal model. It is important to note that the inhibitory effect of SOM230 was relatively selective for GH and IGF-I in that insulin and glucagon secretion was inhibited only at higher doses of SOM230. This lack of potent inhibition of insulin and glucagon release was also reflected in the lack of effect on plasma glucose levels. Even after high dose treatment over 126 days no obvious adverse side effects were noticed, including changes in plasma glucose levels. Conclusion: We have identified a novel short synthetic SRIF peptidomimetic, which exhibits high affinity binding to four of the five **human** SRIF receptor subtypes and has potent, long lasting inhibitory effects on GH and IGF-I release. Therefore SOM230 is a promising development candidate for effective GH and IGF-I inhibition and is currently under evaluation in phase 1 clinical trials.

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ACCESSION NUMBER: 2002097945 EMBASE
TITLE: Decreased expression of the **GHRH** receptor gene due to a mutation in a Pit-1 binding site.
AUTHOR: Salvatori R.; Fan X.; Mullis P.E.; Haile A.; Levine M.A.
CORPORATE SOURCE: Dr. R. Salvatori, Division of Endocrinology, Johns Hopkins Univ. Sch. of Medicine, 1830 East Monument Street, no. 333, Baltimore, MD 21287, United States. salvator@jhmi.edu
SOURCE: Molecular Endocrinology, (2002) Vol. 16, No. 3, pp. 450-458.
Refs: 40
ISSN: 0888-8809 CODEN: MOENEN
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020404
Last Updated on STN: 20020404

AB A variety of mutations in the gene encoding the **GHRH** receptor (GHRHR) that are predicted to alter protein structure or function have been recently described in patients with isolated GH deficiency type IB. In the present report we describe a patient with isolated GH deficiency type IB who was heterozygous for two novel mutations in this gene: a missense mutation in codon 329 that replaces lysine with glutamic acid (K329E) and an A→C transversion (position -124) in one of the two sites of the promoter region that binds the pituitary-specific transcription factor Pit-1, which is required for GHRHR expression. Chinese hamster ovary cells that were transfected with a cDNA encoding the K329E GHRHR expressed the receptor but failed to show a cAMP response after treatment with **GHRH**, confirming the lack of functionality. To test the effect of the A→C mutation at position -124 of the promoter, we transfected rat GH3 pituitary cells, which express endogenous Pit-1, with plasmids in which the luciferase reporter gene was under the control of either the wild-type or the mutant promoter. GH3 cells expressing the mutant promoter showed significantly less luciferase activity than cells expressing the wild-type promoter. DNA-binding studies confirmed that the A→C base change markedly reduces DNA binding to the Pit-1 protein. These results demonstrate that mutations in the GHRHR are not limited to the coding sequence and that promoter

mutations that impair Pit-1 binding can reduce expression of the GHRHR gene.

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ACCESSION NUMBER: 2002095213 EMBASE
TITLE: Isolated growth hormone (GH) deficiency due to compound heterozygosity for two new mutations in the GH-releasing hormone receptor gene.
AUTHOR: Salvatori R.; Fan X.; Phillips III J.A.; Prince M.; Levine M.A.
CORPORATE SOURCE: Dr. R. Salvatori, Division of Endocrinology, Johns Hopkins Univ. Sch. of Medicine, 1830 East Monument Street, Baltimore, MD 21287, United States. salvator@jhmi.edu
SOURCE: Clinical Endocrinology, (2001) Vol. 54, No. 5, pp. 681-687.
Refs: 30
ISSN: 0300-0664 CODEN: CLENAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020328
Last Updated on STN: 20020328

AB OBJECTIVE: Mutations in the GH releasing hormone receptor (**GHRH**-R) have recently been shown to cause autosomal recessive isolated GH deficiency (IGHD). Patients who are homozygous for **GHRH**-R mutations have a subnormal GH response to pharmacological agents that stimulate GH secretion and an appropriate response to exogenous GH therapy. We searched for mutations in the **GHRH**-R gene in a family in which two of three siblings were affected by IGHD. DESIGN: We sequenced the 13 coding exons, the intron-exon boundaries and 327 bases of the promoter of the **GHRH**-R gene from peripheral blood cell genomic DNA of an index patient. RESULTS: Both affected individuals were compound heterozygotes for two previously undescribed **GHRH**-R mutations: a change in codon 137 that replaces histidine with leucine (H137L), and a 5 bp deletion in exon 11 (Del 1140-1144). The patients' father was heterozygous for the H137L mutation, and the mother was heterozygous for the exon 11 deletion. We used site-directed mutagenesis to create the mutants in wild-type **GHRH**-R cDNA. Transient transfection of **GHRH**-R cDNAs in Chinese hamster ovary cells showed that cells transfected with both mutant receptors failed to increase cyclic AMP after treatment with **GHRH**. CONCLUSIONS: We describe a family in which two siblings with IGHD were compound heterozygotes for two new mutations in the **GHRH**-R gene. These results suggest that mutant alleles for **GHRH**-R gene may be more common than previously suspected.

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ACCESSION NUMBER: 2002088028 EMBASE
TITLE: Molecular analysis of the **growth hormone releasing hormone** receptor gene (**GHRH**-R) in isolated growth hormone deficiency: Identification of a likely etiological mutation in the signal peptide.
AUTHOR: Lessi M.; Giordano M.; Paracchini R.; Petri A.; Federico G.; Wasniewska M.; Pasquino A.M.; Aimaretti G.; Bona G.; Momigliano-Richiardi P.
CORPORATE SOURCE: M. Giordano, Dipartimento Scienze Mediche, via Solaroli 17, 28100 Novara, Italy. giordano@med.unipmn.it
SOURCE: Journal of Endocrine Genetics, (2001) Vol. 2, No. 4, pp. 215-228.
Refs: 40
ISSN: 1565-012X CODEN: JEGEF6
COUNTRY: Israel

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020321
Last Updated on STN: 20020321

AB The coding sequence, the intron-exon boundaries and the proximal promoter of the **growth hormone releasing hormone** receptor gene (**GHRH**-R) were screened for sequence variations in 22 unrelated Italian patients with isolated growth hormone deficiency (IGHD). Six single nucleotide variations were detected in the 5' flanking region, five in the intronic sequences and five leading to **amino acid substitutions**. All the variations had comparable frequencies in the patients and in controls except for T29C, leading to a Val10Gly substitution in the signal peptide, which was present in the heterozygous state in one patient and was never detected in 1,226 control chromosomes. Gly has different physio-chemical properties from Val and Ile commonly present in the homologous position in closely related species, and it is never found in the corresponding position of eukaryotic signal peptides. Thus this missense substitution might represent a new IGHD etiological dominant mutation acting through a pathophysiological mechanism involving the signal peptide.

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ACCESSION NUMBER: 2001407707 EMBASE
TITLE: Ectopic secretion of **growth hormone-releasing hormone** (**GHRH**) in neuroendocrine tumors: Relevant clinical aspects.
AUTHOR: Doga M.; Bonadonna S.; Burattin A.; Giustina A.
CORPORATE SOURCE: Dr. A. Giustina, Endocrine Section 2a Medicina, Spedali Civili di Brescia, 25125 Brescia, Italy. giustina@master.cci.unibs.it
SOURCE: Annals of Oncology, (2001) Vol. 12, No. SUPPLE. 2, pp. S89-S94.
Refs: 54
ISSN: 0923-7534 CODEN: ANONE2
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20011206
Last Updated on STN: 20011206

AB The aim of this article is to briefly review the physiology of **growth hormone-releasing hormone** (**GHRH**) and the diagnosis and treatment of **GHRH**-mediated acromegaly. Moreover, the role of **GHRH** and its antagonists in the pathogenesis and treatment of cancer will be reviewed. Hypothalamic **GHRH** is secreted into the portal system, binds to specific surface receptors of the somatotroph cell and elicits intracellular signals that modulate pituitary GH synthesis and/or secretion. **GHRH** -producing neurons have been well characterized in the hypothalamus by immunostaining techniques. Hypothalamic tumors, including hamartomas, choristomas, gliomas, and gangliocitomas, may produce excessive **GHRH** with subsequent GH hypersecretion and resultant acromegaly. **GHRH** is synthesized and expressed in multiple extrapituitary tissues. Excessive peripheral production of **GHRH** by a tumor source would therefore be expected to cause somatotroph cell hyperstimulation and increased GH secretion. The structure of hypothalamic **GHRH** was infact elucidated from material extracted

from pancreatic **GHRH**-secreting tumors in two patients with acromegaly. Immunoreactive **GHRH** is present in several tumors, including carcinoid tumors, pancreatic cell tumors, small-cell lung cancers, adrenal adenomas, and pheochromocitomas which have been reported to secrete **GHRH**. Acromegaly in these patients, however, is uncommon. In a retrospective survey of 177 acromegalic patients only a single patient was identified with elevated plasma **GHRH** levels. Measuring **GHRH** plasma levels therefore provides a precise and cost-effective test for the diagnosis of ectopic acromegaly. Peripheral **GHRH** levels are not elevated in patients with hypothalamic **GHRH**- secreting tumors, supporting the notion that excess eutopic hypothalamic **GHRH** secretion into the hypophyseal portal system does not appreciably enter the systemic circulation. Elevated circulating **GHRH** levels, a normal or small-size pituitary gland, or clinical and biochemical features of other tumors known to be associated with extrapituitary acromegaly, are all indications for extrapituitary imaging. An enlarged pituitary is, however, often found on MRI of patients with peripheral **GHRH**-secreting tumors, and the radiologic diagnosis of a pituitary adenoma may be difficult to exclude. Surgical resection of the tumor secreting ectopic **GHRH** should reverse the hypersecretion of GH, and pituitary surgery should not be necessary in these patients. Nonresectable, disseminated or reccurrent carcinoid syndrome with ectopic **GHRH** secretion can also be managed medically with long-acting somatostatin analogs (octreotide and lanreotide). The presence of **GHRH** and its receptors in several extrahypothalamic tissues, including ovary, testis and the digestive tract, suggests that **GHRH** may have a regulatory role in these tissues. As previously mentioned, biologically or immunologically active **GHRH** and mRNA encoding **GHRH** have been found in several **human** malignant tumors, including cancers of the breast, endometrium and ovary and their cell lines. The synthesis and evaluation of analogs with various modifications revealed that certain hydrophobic and helix-stabilizing **amino acid substitutions** can produce antagonists with increased GH releasing inhibitory potencies and **GHRH** receptor-binding affinities in vitro. The review of experimental results of these substances are promising altrough no clinical data are yet available. Finally, the advent of these antagonists has allowed significant progress in the understanding of the role of the central and tissue **GHRH**-GH-IGFs system in the pathogenesis of tumors.

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(Y)/N:y

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on STN

ACCESSION NUMBER: 2001129896 EMBASE

TITLE: Molecular cloning of **growth hormone-releasing hormone**/pituitary adenylyl cyclase-activating polypeptide in the frog Xenopus laevis: Brain distribution and regulation after castration.

AUTHOR: Hu Z.; Lelievre V.; Tam J.; Cheng J.W.; Fuenzalida G.; Zhou X.; Waschek J.A.

CORPORATE SOURCE: Dr. J.A. Waschek, Department of Psychiatry, University of California, 760 Westwood Plaza, Los Angeles, CA 90024, United States. jwaschek@mednet.ucla.edu

SOURCE: Endocrinology, (2000) Vol. 141, No. 9, pp. 3366-3376.
Refs: 57
ISSN: 0013-7227 CODEN: ENDOAO

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 003 Endocrinology
008 Neurology and Neurosurgery

022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20010419
Last Updated on STN: 20010419

AB Pituitary adenylyl cyclase-activating peptide (PACAP) appears to regulate several neuroendocrine functions in the frog, but its messenger RNA (mRNA) structure and brain distribution are unknown. To understand the potential role of PACAP in the male frog hypothalamic-pituitary-gonadal axis, we cloned the frog Xenopus laevis PACAP mRNA and determined its distribution in the brain. We then analyzed the castration-induced alterations of mRNA expression for PACAP and its selective type I receptor (PAC(1)) in the hypothalamic anterior preoptic area, a region known to regulate reproductive function. The PACAP mRNA encodes a peptide precursor predicted to give rise to both GH-releasing hormone and PACAP. The deduced peptide sequence of PACAP-38 was nearly identical to that of **human** PACAP with one **amino acid substitution**. Abundant PACAP mRNA was detected in the brain, but not several other tissues, including the testis. In situ hybridization revealed strong expression of the PACAP gene in the dorsal pallium, ventral hypothalamus, and nuclei of cerebellum. PACAP mRNA signals were weak to moderate in the hypothalamic anterior preoptic area and were absent in the pituitary. Castration induced an increase in the expression of PACAP and PAC(1) receptor mRNAs in the hypothalamic anterior preoptic area after 3 days. Replacement with testosterone prevented the castration-induced changes. These results provide a molecular basis for studying the physiological functions of PACAP in frog brain and suggest that PACAP may be involved in the feedback regulation of hypothalamic-pituitary-gonadal axis.

L9 ANSWER 42 OF 53 EMBASE
on STN
ACCESSION NUMBER: 2001046531 EMBASE
TITLE: Three new mutations in the gene for the growth hormone (GH)-releasing hormone receptor in familial isolated GH deficiency type IB.
AUTHOR: Salvatori R.; Fan X.; Phillips III J.A.; Espigares-Martin R.; De Lara I.M.; Freeman K.L.; Plotnick L.; Al-Ashwal A.; Levine M.A.
CORPORATE SOURCE: Dr. R. Salvatori, Division of Endocrinology, Johns Hopkins University, School of Medicine, 1830 East Monument Street, No. 333, Baltimore, MD 21287, United States.
salvator@jhmi.edu
SOURCE: Journal of Clinical Endocrinology and Metabolism, (2001) Vol. 86, No. 1, pp. 273-279.
Refs: 41
ISSN: 0021-972X CODEN: JCEMAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20010223
Last Updated on STN: 20010223

AB Isolated GH deficiency (IGHD) is familial in 5-30% of cases. The majority of patients have the type IB form, characterized by autosomal recessive transmission, low but measurable serum concentrations of GH, and responsiveness to exogenous GH therapy. Unique mutations in the gene encoding the **GHRH** receptor (GHRHR) have previously been described in 2 kindreds with IGHD IB. However, the prevalence of GHRHR mutations in patients with IGHD IB is unknown. We analyzed 30 families with IGHD IB in which more than i member was affected. Linkage analysis was performed in 28 of the families, and in 3 families sibling pair analysis indicated linkage to the GHRHR gene locus. These 3 families as

well as 2 families in which linkage analysis was not performed were screened for mutations in the 13 coding exons, the intron-exon boundaries, and 327 bases of the promoter of the GHRHR gene. We identified novel GHRHR missense mutations in 2 of the 3 kindreds with informative linkage and in 1 family in which linkage had not been performed. In 1 family affected members were homozygous for a mutation in codon 144 that replaces leucine with histidine (L144H). Affected subjects in a second family were compound heterozygotes, carrying both the L144H mutation and a second mutation in codon 242 that replaces phenylalanine with cysteine. Affected subjects in a third family were homozygous for a mutation that replaces alanine at codon 222 with glutamic acid. All 3 mutations segregated with the IGHD phenotype. All 3 mutant receptors were expressed in CHO cells, and each failed to show a cAMP response after treatment of the cells with **GHRH**. These results demonstrate that missense mutations in the GHRHR gene are a cause of IGHD IB, and that defects in the GHRHR gene may be a more common cause of GH deficiency than previously suspected.

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ACCESSION NUMBER: 1998093908 EMBASE
TITLE: Genetic defects in the control of growth hormone secretion.
AUTHOR: Gertner J.M.; Wajnrajch M.P.; Leibel R.L.
CORPORATE SOURCE: Prof. J.M. Gertner, Department Research and Development, Serono Laboratories Inc, 100 Longwater Circle, Norwell, MA 02061, United States
SOURCE: Hormone Research, (1998) Vol. 49, No. SUPPL. 1, pp. 9-14. Refs: 30
ISSN: 0301-0163 CODEN: HRMRA3
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 003 Endocrinology
007 Pediatrics and Pediatric Surgery
022 Human Genetics
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19980409
Last Updated on STN: 19980409

AB Since growth hormone deficiency (GHD) causes short stature and metabolic derangements, the processes which control its release are important physiologically. These processes can be illuminated by an understanding of genetically determined GHD. In 2 Indian Moslem cousins from a consanguineous family, GHD resistant to **growth hormone releasing hormone** (**GHRH**) stimulation was found. No mutations were found in the growth hormone gene (GH1) (J. Phillips). The receptor for **GHRH** (GHRHR), implicated in the dwarfism of the little mouse, thus becomes a candidate gene to explain their GHD. Amplification and sequencing a region of GHRHR homologous to that mutated in the little mouse showed a mutation (265G*T) leading to a stop codon at position 72 which would completely prevent GHRHR expression. Subsequently, Maheshwari et al, found an identical mutation in a multiplex kindred from Sindh, Pakistan, about 800 km from the place of origin of our patients. GHD is more commonly caused by recessive or dominant mutations of GH1. The latter are of great interest in understanding the mechanism of GH secretion. In a large kindred with dominant GHD we found a heterozygous 666G*A mutation replacing of Arg with His at amino acid 183. We speculate that the introduced histidine interferes with interactions necessary for correct GH secretion.

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ACCESSION NUMBER: 1998062313 EMBASE
TITLE: In vitro thyrotropin-releasing activity of corticotropin-releasing hormone-family peptides in coho salmon, Oncorhynchus kisutch.
AUTHOR: Larsen D.A.; Swanson P.; Dickey J.T.; Rivier J.; Dickhoff W.W.

contribute to their increased biological activity. **GHRH**-(1-29)-NH2 and D-Ala2-**GHRH**-(1-29)-NH2 were administered by constant iv infusion at a rate of 25 ng/kg · min to 10 normal men. Blood was sampled during the 90 min infusion and for 20 min afterward and assayed for the infused analog. The MCR of the D-Ala2 analog (mean ± SE) was significantly less (21 ± 1.2 mL/kg · min) than that of **GHRH**-(1-29)-NH2 (39.7 ± 3.9 mL/kg · min; $P < 0.001$). The disappearance half-time of the D-Ala2 analog was 6.7 ± 0.5, whereas that of **GHRH**-(1-29)- NH2 was 4.3 ± 1.4 min ($P < 0.05$). These findings demonstrate that the D- Ala2 substitution contributes to the enhancement of biological activity by reducing metabolic clearance.

L9 ANSWER 48 OF 53 EMBASE
on STN

ACCESSION NUMBER: 93224343 EMBASE
DOCUMENT NUMBER: 1993224343
TITLE: Two salmon neuropeptides encoded by one brain cDNA are structurally related to members of the glucagon superfamily.
AUTHOR: Parker D.B.; Coe I.R.; Dixon G.H.; Sherwood N.M.
CORPORATE SOURCE: Department of Biology, University of Victoria, P.O. Box 1700,Victoria, BC V8W 2Y2, Canada
SOURCE: European Journal of Biochemistry, (1993) Vol. 215, No. 2, pp. 439-448.
ISSN: 0014-2956 CODEN: EJBCAI
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 930829
Last Updated on STN: 930829

AB A cDNA that codes for two peptides in the glucagon superfamily has been isolated from sockeye salmon brain. The first peptide is related to **growth hormone-releasing hormone** (**GHRH**), which has high sequence similarity with PACAP-related peptide. The second peptide is structurally related to vasoactive intestinal peptide, which is also related to a newly identified peptide in mannals, pituitary adenylate-cyclase-activating polypeptide (PACAP). The salmon precursor contains 173 amino acids and has dibasic and monobasic enzyme-processing sites for cleavage of a 45-aminoacid **GHRH**-like peptide with a free C-terminus and a 38-amino-acid PACAP with an amidated C-terminus. The salmon **GHRH**-like peptide has 40% amino acid sequence identity with the **human GHRH** and 56% identity with **human** PACAP-related peptide. The 38-amino-acid salmon PACAP is highly conserved (89 - 92% identity) with only three or four **amino acid substitutions** compared with the **human, ovine** and rat 38-amino-acid PACAP. Not previously reported for mammalian species, a short precursor coding for only one peptide exists in salmon in addition to the long precursor coding for two peptides. In the short precursor, the coding region for **GHRH** is deleted leaving the PACAP-coding region in a correct reading frame. This provides one possible control mechanism for an increased expression of one peptide (PACAP) without the concomitant increase in the other peptide (**GHRH**) as occurs in a double-peptide precursor. The importance of the 3' non-translated region of the salmon **GHRH**/PACAP precursor in the regulation of translation is suggested by its 70% nucleotide sequence identity to the 3' non-translated regions of the mammalian PACAP precursors. The structural organization of the salmon **GHRH**/PACAP precursor provides a possible evolutionary scheme for precursors that contain tandem peptides in the glucagon superfamily.

L9 ANSWER 49 OF 53 EMBASE
on STN

ACCESSION NUMBER: 93195807 EMBASE
DOCUMENT NUMBER: 1993195807

CORPORATE SOURCE: D.A. Larsen, Integrative Fish Biology Laboratory, Northwest Fisheries Science Center, 2725 Montlake Boulevard East, Seattle, WA 98112, United States
SOURCE: General and Comparative Endocrinology, (1998) Vol. 109, No. 2, pp. 276-285.
Refs: 67
ISSN: 0016-6480 CODEN: GCENA5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
021 Developmental Biology and Teratology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19980320
Last Updated on STN: 19980320

AB Investigations of hypothalamic regulation of fish thyrotropin (TSH) secretion and subsequent thyroid activity have been impeded by the lack of a reliable assay for TSH. Using a recently developed radioimmunoassay (RIA) for coho salmon TSH we employed an in vitro pituitary cell culture technique to examine regulation of TSH secretion by corticotropin-releasing hormone (CRH) family peptides [**ovine** CRH (oCRH), carp urotensin I (UI), and frog sauvagine (SV)] as well as thyrotropin-releasing hormone (TRH), salmon **growth hormone-releasing hormone** (sGHRH), and salmon gonadotropin-releasing hormone (sGnRH). At concentrations of 0.01 to 100 nM, TRH, sGHRH, and sGnRH did not stimulate TSH secretion from coho salmon pituitary cells. However, at these same concentrations, both oCRH and SV caused a significant and concentration- dependent increase in TSH secretion; whereas, UI was highly stimulatory at all concentrations tested. In a related experiment we examined the effect of α-helical CRF((9-41)) on oCRH-stimulated TSH release by pituitary cells. α-Helical CRF((9-41)) is an analogue of CRH that has been shown by others to antagonize the adrenocorticotropic hormone (ACTH)-releasing activity of CRH in goldfish. Preincubation of cells with 1 M α-helical CRF((9-41)) for 4 h caused a significant suppression of the TSH-releasing activity of oCRH at 1.0 and 10 nM concentrations. The results of these experiments demonstrate the potency of a CRH-like peptide in the hypothalamic regulation of TSH in fish and reveal similarities in the inhibition of the response of both the thyroid and interrenal axis of fish to α-helical CRF((9-41)).

L9 ANSWER 45 OF 53 EMBASE
on STN
ACCESSION NUMBER: 97039847 EMBASE
DOCUMENT NUMBER: 1997039847
TITLE: Structural simplification of potent **growth hormone-releasing hormone** analogs: Implications for other members of the VIP/**GHRH**/PACAP family.
AUTHOR: Coy D.H.; Jiang N.-Y.; Fuselier J.; Murphy W.A.; Yanaihara N.
CORPORATE SOURCE: D.H. Coy, Peptide Research Laboratories, Department of Medicine, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, LA 70112, United States.
dcoy@tmc.tulane.edu
SOURCE: Annals of the New York Academy of Sciences, (1996) Vol. 805, pp. 149-158.
Refs: 15
ISSN: 0077-8923 CODEN: ANYAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
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Last Updated on STN: 970224

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

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ACCESSION NUMBER: 96025340 EMBASE
DOCUMENT NUMBER: 1996025340
TITLE: Identification of a new G-protein-linked receptor for growth hormone secretagogues.
AUTHOR: Pong S.-S.; Chaung L.-Y.P.; Dean D.C.; Nargund R.P.; Patchett A.A.; Smith R.G.
CORPORATE SOURCE: Biochemistry/Physiology Department, Merck Research Laboratories, P.O. Box 2000,Rahway, NJ 07065, United States
SOURCE: Molecular Endocrinology, (1996) Vol. 10, No. 1, pp. 57-61.
ISSN: 0888-8809 CODEN: MOENEN
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 960206
Last Updated on STN: 960206

AB The potential application of small molecules in GH therapy has recently become a topic of increasing interest. The spiroindoline MK-0677, the benzolactam L-692,429, and the peptides, GHRP-6 and hexarelin, have been shown to possess potent and selective GH-secretory activity in several species including **human**. Moreover, these synthetic GH secretagogues act on a signal transduction pathway distinct from that of **GHRH**. A specific high affinity binding site in porcine and rat anterior pituitary membranes that mediates the activity of these secretagogues has now been identified. The binding affinity of these structurally diverse secretagogues is tightly correlated with GH-secretory activity. The binding is Mg2+-dependent, is inhibited by GTP-γ-S, and is not displaced by **GHRH** and somatostatin. The receptor is distinct from that for **GHRH** and has the properties of a new G-protein-coupled receptor. It is speculated that these GH secretagogues mimic an unidentified natural hormone that regulates GH secretion in concert with **GHRH** and somatostatin.

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ACCESSION NUMBER: 94334509 EMBASE
DOCUMENT NUMBER: 1994334509
TITLE: Incorporation of D-Ala2 in **growth hormone -releasing hormone**-(1-29)-NH2 increases the half-life and decreases metabolic clearance in normal men.
AUTHOR: Soule S.; King J.A.; Millar R.P.
CORPORATE SOURCE: Cobbold Laboratories, Middlesex Hospital Medical School, Mortimer Street,London W1N 8AA, United Kingdom
SOURCE: Journal of Clinical Endocrinology and Metabolism, (1994) Vol. 79, No. 4, pp. 1208-1211.
ISSN: 0021-972X CODEN: JCEMAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 941207
Last Updated on STN: 941207

AB D-Ala2-**GHRH**-(1-29) has increased binding affinity and exhibits enhanced biological activity in man. It is not known whether changes in the metabolic clearance of this and other **GHRH** analogs

TITLE: G-proteins and hormonal signalling in **human** pituitary tumors: Genetic mutations and functional alterations.
AUTHOR: Spada A.; Vallar L.; Faglia G.
CORPORATE SOURCE: Institute of Endocrine Sciences, Pad. Granelli, Ospedale Maggiore IRCCS, via F. Sforza 35,20122 Milano, Italy
SOURCE: Frontiers in Neuroendocrinology, (1993) Vol. 14, No. 3, pp. 214-232.
ISSN: 0091-3022 CODEN: FNEDA7
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
008 Neurology and Neurosurgery
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 930808
Last Updated on STN: 930808

AB In the last few years, molecular studies on pituitary adenomas have yielded several lines of evidence supporting a primary pituitary origin for these tumors. In fact, analyses of x-chromosomal inactivation show that the great majority of pituitary tumors are monoclonal in origin, suggesting that one or more mutations are responsible for the selective expansion of a single cell clone. Mutations constitutively activating GTP-binding proteins have been identified in subsets of pituitary adenomas. Single **amino acid substitutions** replacing Arg 201 with either Cys, His, or Gln 227 with either Arg or Leu of the α-subunit of the Gs gene were identified in one third of growth hormone (GH)-secreting adenomas. Both mutations stabilize αs in its active conformation by inhibiting GTPase activity, thus mimicking the effect of specific extracellular growth factors, such as **growth hormone releasing hormone** (**GHRH**). Since several lines of evidence suggest that cAMP is involved in somatotrope replication, it has been proposed that the αs gene can be converted into an oncogene, designated gsp (for Gs protein). Recently, the ras oncogene has been identified in one prolactinoma characterized by unusual invasiveness. Although these data seem to negate a primary role for hypothalamic neurohormones in adenoma formation, it is conceivable that the hormones may exert a role in the sequence of events leading to clonal expansion of a transformed cell. Moreover, alterations in receptor and/or postreceptor events triggered by hypothalamic neurohormones may result in amplification of stimulatory inputs and impairment of inhibitory ones.

L9 ANSWER 50 OF 53 EMBASE on STN
ACCESSION NUMBER: 92163896 EMBASE
DOCUMENT NUMBER: 1992163896
TITLE: Evaluation of the biological potency of new agmatine analogs of **growth hormone-releasing hormone** in the **bovine** .
AUTHOR: Roberge S.; Johnson H.E.; Zarandi M.; Schally A.V.; Reeves J.J.
CORPORATE SOURCE: Dept. of Animal and Poultry Science, University of Guelph,Guelph, Ont. N1G 2W1, Canada
SOURCE: Proceedings of the Society for Experimental Biology and Medicine, (1992) Vol. 200, No. 1, pp. 109-114.
ISSN: 0037-9727 CODEN: PSEBAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 920628
Last Updated on STN: 920628

AB Four new **growth hormone-releasing hormone** (**GHRH**) analogs with C-terminal agmatine were compared with the parent **human GHRH**(1-29)NH2 fragment to assess their abilities to increase serum concentrations of growth hormone (GH) in the **bovine**. The four analogs were: [D-Ala2, Nle27] **GHRH**(1-28)Agm (JG-73); [desNH2-Tyr1, Ala15, Nle27] **GHRH**(1-28)Agm (MZ-2-51); [desNH2- Tyr1, Ala15, D-Lys21, Nle27] **GHRH**(1-28)Agm (MZ-2-75); and [desNH2- Tyr1, D-Lys12,21, Ala15, Nle27] **GHRH**(1-28)Agm (MZ-2-87). The special characteristic of all four **GHRH** analogs is that arginine was replaced by agmatine (Agm) in Position 29. Five pregnant Holstein **cows** received these peptides subcutaneously at the following doses: 0.0156, 0.0625, 0.25, 1, and 4 μg/kg body weight Each **cow** received each analog-dose combination according to a 5 x 5 Greco-Latin square design repeated for the 5-week treatment. Each **cow** also received saline vehicle only at the end of the 5-week treatment. Blood samples were collected from 30 min before until 360 min after treatment injection. Total area under the GH response curves for the 6-hr sampling period for each dose of each **GHRH** analog was compared. There was a linear dose-dependent GH release in response to hGHRH(1-29)NH2 and its four **GHRH**(1- 28)Agm analogs. At the dose of 0.25 μg/kg, two **GHRH** analogs, JG-73 and MZ-2- 75, stimulated greater GH release than hGHRH(1-29)NH2 ($P < 0.05$). No differences were seen at the two lowest doses, 0.0625 and 0.156 μg/kg. When both total area under the GH response curves and GH peak amplitudes for each treatment were averaged for all doses, JG-73 and MZ-2-75 stimulated greater GH release than hGHRH(1-29)NH2 ($p < 0.05$). In summary, three **GHRH**(1-28)Agm analogs, JG-73, MZ-2-75, and MZ-2-51, were found to be 11.8, 11.3, and 6.5 times more potent, respectively, on a weight basis, than hGHRH(1-29)NH2 in stimulating the release of GH in **cows**.

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ACCESSION NUMBER: 91028433 EMBASE
DOCUMENT NUMBER: 1991028433
TITLE: Synthesis and in vitro and in vivo activity of analogs of **growth hormone-releasing hormone** (GH-RH) with C-terminal agmatine.
AUTHOR: Zarandi M.; Csernus V.; Bokser L.; Bajusz S.; Groot K.; Schally A.V.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Administration Medical Center, 1601 Perdido Street, New Orelans, LA 70146, United States
SOURCE: International Journal of Peptide and Protein Research, (1990) Vol. 36, No. 6, pp. 499-505.
ISSN: 0367-8377 CODEN: IJPPC3
COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 911216
Last Updated on STN: 911216

AB In the search for more active analogs of **human growth hormone-releasing hormone** (GH-RH), 37 new compounds were synthesized by solid phase methodology, purified, and tested biologically. Most of the analogs contained a sequence of 27 amino acids and N-terminal desaminotyrosine (Dat) and C-terminal agmatine (Agm), which are not amino acids. In addition to Dat in position 1 and Agm in position 29, the majority of the analogs had Ala15 and Nle27 substitutions and one or more additional L- or D-amino acid modifications. [Dat1, Ala15, Nle27]GH-RH(1-28)Agm (MZ-2-51) was the most active analog. Its in vitro GH-releasing potency was 10.5 times higher than that of GH-RH(1-29)NH2 and in the i.v. in vivo assay, MZ-2-51 was 4-5 times more active than the standard. After s.c. administration to rats, MZ-2-51 showed an activity 34 times higher at 15 min and 179 times greater at 30 min than

GH-RH(1-29)NH2 and also displayed a prolonged activity. D-Tyr10, D-Lys12, and D-Lys21 homologs of MZ-2-51 also showed enhanced activities. Thus, [Dat1, D-Tyr10, Ala15, Nle27]GH-RH(1-28)Agm (MZ-2-159), [Dat1, D-Lys12, Ala15, Nle27]GH-RH(1-28)AGM (MZ-2-57), and [Dat1, Ala15, D-Lys21, Nle27]GH-RH(1-28)Agm (MZ-2-75) were 4-6 times more active in vitro than GH-RH(1-29)NH2. In vivo, after i.v. administration, analog MZ-2-75 was equipotent and analogs MZ-2-159 and MZ-2-57 about twice as potent as the standard. After s.c. administration, the potencies of MZ-2-57 and MZ-2-75 were 10-14 times higher than the standard at 15 min and 45-89 times greater when determined at 30 min. Most of the analogs containing two or more D-**amino acid substitutions** were less active than GH-RH(1-29)NH2 or inactive. Our studies indicate that very potent GH-RH analogs can result from the combination of agmatine in position 29 with other substitutions.

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ACCESSION NUMBER: 89124147 EMBASE
DOCUMENT NUMBER: 1989124147
TITLE: Dipeptidylpeptidase IV and trypsin-like enzymatic degradation of **human growth hormone-releasing hormone** in plasma.
AUTHOR: Frohman L.A.; Downs T.R.; Heimer E.P.; Felix A.M.
CORPORATE SOURCE: Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH 45267, United States
SOURCE: Journal of Clinical Investigation, (1989) Vol. 83, No. 5, pp. 1533-1540.
ISSN: 0021-9738 CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 911212
Last Updated on STN: 911212

AB The plasma enzyme responsible for primary proteolytic cleavage of **growth hormone-releasing hormone** (GRH) at the 2-3 amino acid bond was characterized. Native GRH[GRH(1-44)-NH2 and GRH(1-40)-OH], and COOH-terminally shortened fragments [GRH(1-32)-NH2 and GRH(1-29)-NH2] were rapidly cleaved, while GRH(2-32)-NH2 was not degraded at this site. Moreover, degradation to GRH(3-44)-NH2 was unaffected by an aminopeptidase inhibitor, indicating that this metabolite was generated from a single step cleavage by a dipeptidylpeptidase (DPP) rather than sequential aminopeptidase cleavages. Conversion to GRH(3-44)-NH2 was blocked by diprotin A, a DPP type IV (DPP IV) competitive inhibitor. D-**Amino acid substitution** at either position 1 or 2 also prevented hydrolysis, characteristic of DPP IV. Analysis of endogenous plasma GRH immunoreactivity from a **human** GRH transgenic pig revealed that the major peak coeluted with GRH(3-44)-NH2. Native GRH exhibited trypsin-like degradation at the 11-12 position but cleavage at the 12-13 site occurred only with GRH(1-32)-NH2 and GRH(1-29)-NH2. Formation of these metabolites was independent of prior DPP IV hydrolysis but was greatly reduced by trypsin inhibitors. Evaluation of plasma stability of potential GRH super analogues, designed to resist degradation by these enzymes, confirmed that GRH degradation in plasma occurs primarily by DPP IV, and to a lesser extent by trypsin-like enzyme(s).

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ACCESSION NUMBER: 87038149 EMBASE
DOCUMENT NUMBER: 1987038149
TITLE: The effect of intravenous, subcutaneous, and intranasal GH-RH analog, [Nle27]**GHRH**(1-29)-NH2, on growth

hormone secretion in normal men: Dose-response relationships.

AUTHOR: Vance M.L.; Evans W.S.; Kaiser D.L.; et al.
CORPORATE SOURCE: Department of Internal Medicine, University of Virginia Medical Center, Charlottesville, VA 22908, United States

SOURCE: Clinical Pharmacology and Therapeutics, (1986) Vol. 40, No. 6, pp. 627-633.
CODEN: CLPTAT
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
003 Endocrinology
LANGUAGE: English
ENTRY DATE: Entered STN: 911211
Last Updated on STN: 911211

AB A 29 amino acid analog of **growth hormone releasing hormone** (GH-RH)-40 was given intravenously, subcutaneously, and intranasally to normal men to determine its effectiveness in stimulating growth hormone (GH) release. The GH-RH analog, [Nle27]GH-RH(1-29)-NH2, is an amidated 29 amino acid peptide that has one **amino acid substitution** at position 27. This peptide stimulates GH secretion when given by the intravenous, subcutaneous, and intranasal routes without adverse effect. The degree of GH stimulation was variable among subjects and the greatest amount of stimulation occurred with the highest doses. GH stimulation occurred in a dose-responsive manner after all three routes of administration. A tenfold higher subcutaneous dose was required to stimulate a comparable amount of GH secretion as compared with intravenous administration, and a thirtyfold higher intranasal than intravenous dose was required to stimulate approximately one fifth the amount of GH release. For comparison, one dose of GH-RH-40, 1 μg/kg, was administered intravenously. GH secretion after 1 μg/kg GH-RH-40 and 1 μg/kg Nle27 GH-RH was comparable between the two groups of subjects. Stimulation of GH secretion by Nle27 GH-RH occurred within 5 minutes of intravenous and within 10 minutes of subcutaneous and intranasal administration; peak GH levels were observed within 30 minutes. GH levels declined and returned to near baseline levels 2 hours after administration of the analog. Since GH-RH-40 has been demonstrated to be effective in stimulating GH release and promoting acceleration of linear growth in GH-deficient children, it is likely that a shorter peptide with full biologic activity such as Nle27 GH-RH may also be effective in the treatment of some children with GH deficiency.